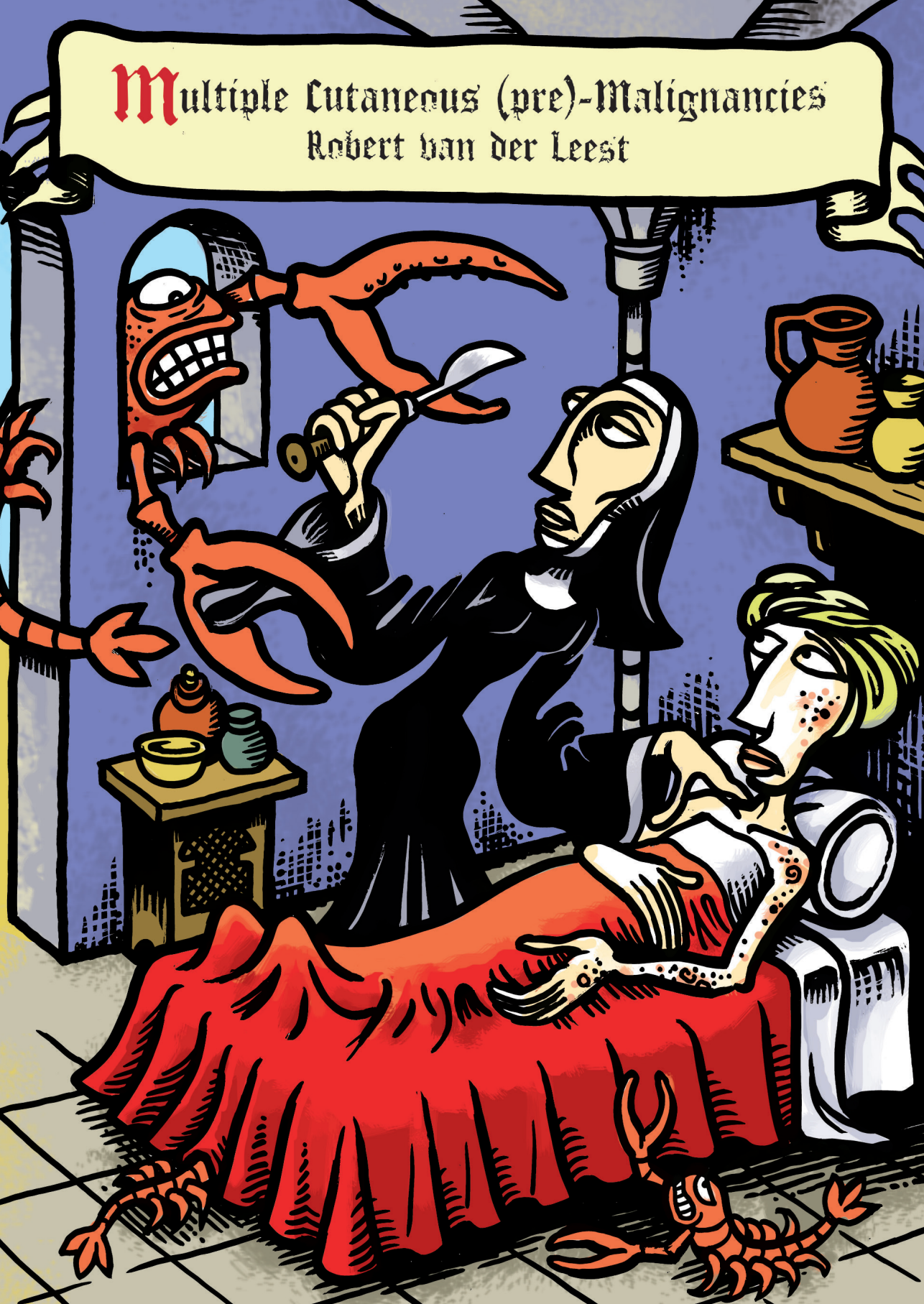
Multiple Cutaneous (pre)-Malignancies
Robert van der Leest

Multiple Cutaneous (pre)-Malignancies

Robert J.T. van der Leest

Netherlands
comprehensive
cancer organisation

The Netherlands Cancer Registry, managed by 'Netherlands comprehensive cancer organisation', was an important data source of the chapters 4, 5, 7, 9 and 10 in this thesis.

ISBN: 978-94-6169-674-8

Cover design: Marcel Ruijters

Cover Font: Puppeteer (copyright 2008 by Tjarda Koster, www.dafont.com, capital letters adapted by Sjoerd Hoeks).

Lay-out and Printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

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Multiple Cutaneous (pre)-Malignancies

Multipele cutane (pre)-maligniteiten

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 24 juni 2015 om 11.30 uur

door

Robertus Josephus Theodorus van der Leest

geboren te Oss

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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‘Voor T&T’

CONTENTS

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CHAPTER 1

Introduction

Skin cancer, the most commonly occurring cancer in Caucasian populations, includes a large number of types of malignancies deriving from a myriad of different cells. The three most common cutaneous malignancies are derived from melanocytes and keratinocytes (ordered in decreasing aggressiveness): melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). This thesis focuses only on these three types of cancer and their precursors. The majority of skin cancer patients have a relatively good prognosis, which has implications for treatment, follow-up strategies and risks of developing multiple cutaneous (pre)-malignancies.

Melanoma, the most aggressive type of skin cancer, develops from the pigment melanin producing melanocytes, derived from the neural crest in origin, which are located in the stratum basale of the skin's epidermis. Melanocytes are also present in eyes, ears, the heart and the central nervous system, but in these organs melanocytes rarely develop into malignant melanomas. Under the influence of ultraviolet radiation melanocytes secrete melanin pigment to numerous keratinocytes by dendritic processes and in this way provide some degree of solar-induced protection of genetic damage to the keratinocytes.

Keratinocyte carcinoma (KC)[1], comprising of SCC and BCC, develops from the epithelial keratinocytes and usually occurs on sun-exposed skin. These cancers are often referred to as non-melanoma skin cancer (NMSC), although technically the non-melanoma skin cancers also encompass cutaneous lymphomas, sarcomas, Merkel cell carcinomas and other rare types of skin cancer[2]. Therefore, in this thesis I will refer to KCs rather than NMSC. BCC, by far the most commonly occurring skin cancer, hardly ever metastasizes (a literature search yielded in total 172 metastatic BCC cases based on criteria of Lattes and Kessler[3], reported between 1981 and 2011, of which 100 metastatic BCC cases included information on follow-up time[4]) and is therefore the most 'benign' type of skin cancer. The majority of BCCs occur on facial skin where their surgical treatment might have a large impact on functional and cosmetic outcome. Cutaneous SCC is known to metastasize if left untreated (proportion of stage III and IV SCC in The Netherlands: 1.5%; 1989-2008[5]). SCC might arise from precursors such as actinic keratosis (AK) and in situ variants (Bowen's disease).

EPIDEMIOLOGY

The incidence rates of the three most common skin cancers are rising and show large variations between countries. Recently a stabilization or decline was found for melanoma patients (mainly younger patients) in Australia, New Zealand, the U.S.A., Canada, Israel and Norway[6,7]. The decline in Australia might have been artificial, due to immigration of people with dark skin types, which have a lower risk of developing skin cancer[8]. In Table 1 trends of incidence rates of The Netherlands, the U.S.A. and Australia were listed, direct comparisons are not possible because age standardized rates were adjusted to different populations (no recent world standardized rates available for U.S.A.). Besides, incidence rates of SCC and BCC in the U.S.A. and Australia were based on surveys[9,10].

In general, the survival of melanoma improved markedly in recent decades (5-year relative survival in The Netherlands; 1989-1993: 81% and 2008-2012: 89%[11]), probably because of improved awareness and early detection of melanoma. The last two decades mortality rates of melanoma were rising, but recent mortality data seem to indicate a stabilizing or decreasing trend (Figure 1; age-standardized mortality rates (per 100,000 person-years) in respectively 1989, 2000, 2010, 2011, 2012 and 2013 were 2.24, 2.71, 3.75, 3.64, 3.63 and 3.72[11]). In the Netherlands, 821 patients died due to melanoma in 2013[11]. Important prognostic factors for melanoma are Breslow thickness, nodal involvement (sentinel node procedure), histologically recognized ulceration, mitotic rate (number of mitosis per mm square)[12], and gender[13].

The survival of SCC was relatively stable (5-year relative survival in The Netherlands; 1989-1993: 91% and 2008-2012: 95%). The relative survival may have been influenced by the increased mortality risk of SCC patients with a history of solid organ transplantation and immunosuppressive drug use. Therefore the relative survival of SCC patients without these conditions may even be higher. Mortality rates remained stable between

Table 1. Incidence of skin cancer in The Netherlands, the U.S.A. and Australia (age standardized rate / 100,000 person-years for males (M) and females (F)).

	The Netherlands	U.S.A.	Australia
Melanoma	1989 (M,F): 7.4, 10.8	1950-1954 (M,F): 1.9, 2.6	1982 (M,F): 22.9, 22.5
	2013 (M,F): 18.9, 21.8[11]*	2003-2007 (M,F): 33.5, 25.3[16]**	2010 (M,F): 44.9, 31.2[17]*
Basal cell carcinoma	1973 (M,F): 27, 22	1977-1978 (M,F): 618.7, 930.3	1985 (M,F): 735, 593
	2008 (M,F): 101, 101[18]*	1998-1999 (M,F): 930.3, 485.5[9]**	2002 (M,F): 1041, 745[10]*
Squamous cell carcinoma	1989 (M,F): 13.7, 5.5	1977-1978 (M,F): 187.5, 356.2	1985 (M,F): 209, 122
	2013 (M,F): 24.1, 16.4[11]*	1998-1999 (M,F): 71.8, 150.4[9]**	2002 (M,F): 499, 291[10]*

Abbreviations: 'M'= males, 'F'= females.

*adjusted to the World Standard Population.

**adjusted to the U.S.A. census Standard Population.

1989 (Mortality rates per 100,000 person-years, adjusted for the European standard population [ESR] 0.45) and 2013 (ESR 0.35). In 2013, an estimated 98 patients died due to SCC in The Netherlands[11].

The survival of BCC is most likely almost 100%, exact numbers are not available for The Netherlands. However, the high incidence of BCC (Table 1), increasing incidence in younger patients[14] and high risks of developing multiple BCCs (5-year cumulative risk of developing one or more subsequent BCCs in The Netherlands is 29.2%[15]) make this type of skin cancer a major public health concern.

The increasing incidence rates of skin cancer together with a small change of mortality rates suggest cancer overdiagnosis of skin cancer. Cancer overdiagnosis may have two explanations: a) the cancer never progresses (or regresses); or b) the cancer progresses slowly enough that the patient dies of other causes before the cancer becomes symptomatic[19]. Three variables are important for the second explanation: cancer size at detection, its growth rate and the patient's competing risks for mortality[19]. Besides, an overdiagnosed patient has a tumor that fulfills the pathological criteria for cancer[19]. Dermatologists are not able to know which patients are overdiagnosed at time of diagnosis and therefore treat all of them. Thus, overdiagnosis contributes to the problem of escalating health-care costs[19]. Besides, overdiagnosis stimulates overdiagnosis and screening because an increasing proportion of the population knows someone who 'owes their life' to early cancer detection, some have labeled this the popularity paradox of screening[19].

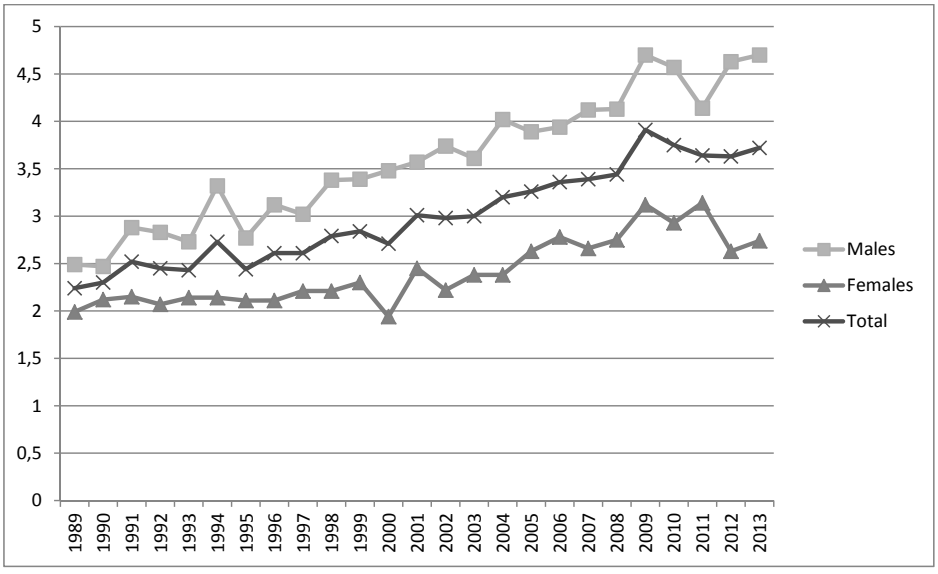

Figure 1. Mortality rates of melanoma in The Netherlands between 1989 and 2013, adjusted for the European standard population (ESR / 100,000 person-years), source: www.dutchcancerfigures.nl/www.statline.nl.

CLINICAL PRESENTATION, HISTOPATHOLOGY, DIAGNOSIS AND TREATMENT (SEE COLOR SECTION)

Melanoma and melanoma in situ

The majority of melanoma patients do not present with full-blown melanomas but with precursor forms, thin melanomas (proportion invasive melanomas with a Breslow thickness of <1mm: 50%[20]) or with concerns about pigmented lesions. It is important to be able to recognize various forms of melanocytic lesions to prevent unnecessary excisions or treatment delay. Melanocytes are found as single dendritic cells surrounded by keratinocytes in the basal layer. In neoplasms melanocytes are found as a group of cells or a nest and then are called nevus cells. Neoplasms of melanocytic origin can be benign, borderline, or malignant. The borderline group is represented by dysplastic nevi. Diagnosis requires multiple architectural and cytologic criteria and is difficult for pathologists because some features can be found in both benign nevi and melanomas[21]. Superficial spreading melanoma (approximately 60% of melanomas in Caucasian populations[20]) usually originates from an atypical melanocytic nevus, but it might arise from normal skin. It has a radial and vertical growth phase and starts with the radial phase. After months to years vertical growth follows. Histology shows large melanocytic cells with nest formation in the dermo-epidermal junction, atypical mitoses, a pagetoid growth pattern and invasion of the dermis by atypical melanocytes. Nodular melanoma (around 15% of melanomas among Caucasians[20]) is a more aggressive form and develops without a radial growth phase de novo or from atypical nevi. Highly atypical melanocytes infiltrate the deep dermis. The less common acral lentiginous melanoma is seen on the palms and soles and under the nails. This form is most prevalent in darker-skinned individuals and Asians. Clinically, lentigo maligna is an irregularly pigmented brownish macule, usually in older patients, which grows radially. Histologically it is a melanoma in situ with atypical melanocytes in the basal layers of the epidermis. After some time the macule can thicken and become an invasive lentigo maligna melanoma (around 3% of melanomas among Caucasians[22]). Melanoma in situ are cancer cells in the epidermis without growth into deeper layers of the skin. It is treated surgically and the life expectancy of patients with melanomas in situ is similar to that of the general population.

Different aspects of a pigmented lesion can be visualized with a dermatoscope evaluating Asymmetry, Border, Color and Differential structures (ABCD rule), pattern analysis, the 7-point checklist, the Menzies method or the revised pattern analysis[23]. A high dermoscopy score leads to a suspicion of malignancy and the lesion should be excised with 2 mm margins and examined histopathologically.

The Breslow thickness is the depth that the melanoma reaches measured from the granular layer in the epidermis and is incorporated in the T staging of the TNM

system[24]. Recommended re-excision margins are determined by Breslow thickness, ranging from 5 mm for in situ melanoma to 20 mm for melanomas with a Breslow thickness higher than 2 mm[25]. In The Netherlands, patients with a melanoma with stage 1B or higher can be referred to a surgical oncologist for a sentinel node procedure[25]. Having a positive sentinel node influences survival greatly and is therefore a major prognostic value, but the sentinel node procedure is considered a prognostic rather than a therapeutic intervention, as the influence of the sentinel node procedure on disease free survival remains subject of debate[26]. Imaging diagnostics are also mainly of prognostic value.

In the past approved agents for advanced melanomas were dacarbazine chemotherapy (1976) and high-dose Interleukin-2 (1998). Recently, several new therapies became available for advanced melanoma patients. In 2011, the immunotherapy ipilimumab (antibody to cytotoxic T-lymphocyte-associated antigen-4) and targeted therapy vemurafenib (BRAF inhibitor) were approved. The BRAF inhibitor dabrafenib and MEK inhibitor trametinib were approved in 2013. Pembrolizumab (antibody to programmed cell death-1, PD-1) was approved in 2014 and nivolumab (antibody to PD-1) may be approved in the near future[27]. Acquired resistance to therapy and efficacy of combination therapies are currently being investigated.

Squamous cell carcinoma, Bowen's disease and actinic keratosis

SCCs have a polymorph-presenting pattern from ulceration to invasive tumors, usually with the presence of hyperkeratosis. The highly prevalent actinic keratoses are precursors of SCC and are found on sun-exposed sites of the body. The risk of progression of a single actinic keratosis to SCC is approximately 0.1% and 60% of SCCs arise from a preexistent actinic keratosis[28], but the problem for clinicians is that the risk of progression of an individual lesion is unknown[29].

AKs may also develop into BCCs, but it is also possible that BCCs are misdiagnosed as AK[30]. Bowen's disease, or squamous cell carcinoma in situ, manifests as a sharply circumscribed erythematous plaque sometimes covered with scales (resembling eczema and psoriasis). The disorder involves full thickness of the epidermis where different degrees of dysplasia can be seen. In contrast with actinic keratosis, atypical squamous cells are present in the whole thickness of the epidermis, but no invasion of the dermis is present. In SCC the basement membrane is destroyed and atypical cells form keratinous pearls invading the dermis with a reduced surrounding stroma containing an inflammatory infiltrate. The majority of SCCs are found on the head. SCCs on ears, lips and anogential region are more likely to produce metastases than tumors on the scalp or face[5,31]. Most metastases are in-transit metastasis (unknown proportion) or draining lymph node metastasis (approximately 10%)[32].

Conventional surgical excision is the first choice in treatment of primary cutaneous SCC (surgical margins depending on tumor size and location)[32]. Mohs micrographic surgery is more appropriate at difficult sites where wide margins could result in functional impairment. Treatment preferences for advanced SCCs should be discussed within multidisciplinary teams. Radiotherapy is a good treatment option for patients with a contra-indication for surgery. AK and Bowen's disease can be treated with nonsurgical treatments like topical 5% 5-fluorouracil cream, imiquimod 5% cream, ingenol mebutate gel, cryotherapy or photodynamic therapy.

Basal cell carcinoma

Early BCCs can be recognized as small, translucent, light-colored papules or nodules of the skin, completely covered by a thin epidermis through which teleangiectasias are noticeable. The tumor slowly evolves into a nodus with a typical pearly aspect and teleangiectasias (nodular type), subsequently ulceration appears. Sometimes the lesion can be pigmented and confusion with a melanoma is possible. The classical ulcus rodens is an extensive nodo-ulcerative BCC. Furthermore, there is a red, scaly superficial type (often misdiagnosed as eczema) and thickened or scar tissue-like infiltrative (morpheaform or micronodular) type. Dermoscopy features of non-pigmented BCCs are arborizing vessels, superficial fine telangiectasia, ulceration, multiple small erosions, shiny white-red structureless areas and short white streaks; pigmented BCCs may also display one or more of the following features: blue-gray ovoid nests, multiple blue-gray dots/globules, in-focus dots, maple leaf-like areas, spoke wheel areas and concentric structures[33]. Diagnosis requires a skin biopsy (diameter 2-3 mm) for histopathological examination, however, in clinical practice some lesions with typical aspects (mainly superficial basal cell carcinoma) are treated without a previous biopsy[34]. Histopathological examination shows epithelial islands, characterized by dark cells with a small volume of cytoplasm surrounded by cells in a palisade arrangement. The cells look similar to the cells of the basal lamina in the epidermis and matrix cells of the adnexa. Superficial BCCs can be treated with imiquimod, 5-fluorouracil, cryosurgery or photodynamic therapy. Other BCCs can be treated with surgical excision (SE), Mohs' micrographic surgery (MMS), radiotherapy, cryosurgery, curettage and electrocoagulation. SE and MMS have the advantage of margin control (MMS aims an almost 100% margin control), other treatment options should be reserved for patients who cannot undergo surgery[35]. Indications for MMS are tumour site localized to the H zone (central face, around the eyes, nose, lips and ears, cosmetically and functionally important areas), tumour size larger than 2 cm, aggressive histopathological subtype (especially morphoeic, infiltrative, micronodular and basosquamous subtypes), poor clinical definition of tumour margins, recurrent lesions, perineural or perivascular involvement[36]. Recently, the long term results of MMS versus surgical excision in patients with respectively high risk facial BCCs or recurrent facial

BCCs were reported with 10-year cumulative recurrence probabilities of 4.4% vs. 12.2% and 3.9% vs. 13.5%[37].

For the small group of patients with locally advanced or metastatic BCC and patients with the basal cell nevus syndrome the new therapy option vismodegib (oral capsules) is available[38,39]. Almost all BCCs have genetic alterations in the hedgehog signaling pathway which causes loss of function of patched homologue 1 (PTCH1), which normally inhibits the signaling activity of smoothened homologue (SMO). Vismodegib is a small-molecule inhibitor of SMO. Response rates in respectively metastatic BCC and locally advanced BCC were 30% and 43% with a median duration of response of 7.6 months in both groups. Approximately 30% had adverse events like muscle spasms, alopecia, dysgeusia, weight loss, and fatigue and 25% reported serious adverse events[39].

CARCINOGENESIS

The understanding of the genetic basis of melanoma has increased markedly in recent years. The well-known BRAF p.V600E classical oncogene has activating mutations in approximately 50% of melanomas and 15-20% have activating mutations in NRAS, in a mutually exclusive way[40]. These oncogenes lead to activation of the RAS RAF MEK ERK mitogen-activated protein kinase (MAPK) pathway. BRAF mutations are characteristic for melanomas which develop on non-chronically sun-exposed skin; in melanomas developed on chronically sun exposed sites BRAF and NRAS mutations are equally distributed. However, 80% of benign nevi have BRAF p.V600E mutations, so other mechanisms are also important in melanoma genesis. Besides, the majority of melanoma patients treated with BRAF inhibitors and an initial response became resistant to therapy. Several mechanisms for these recurrences were suggested and combination therapies are currently investigated[40]. A variety of KIT mutations are found in 2% of skin melanomas (21% in acral melanomas), clinical responses were only observed in patients with specific KIT mutations[40]. New oncogene candidates based on recent studies are MAP2K1/2, MAP3K5, MAP3K9, ERBB4, TRRAP, GRIN2A, GRM3, RAC1, PREX2, HRAS and BRAF amplification[40]. Mutations in the tumor suppressor gene CDKN2A (p16-Leiden) and melanocortin-1 receptor gene (MC1R) variants are also associated with high risks of melanoma[41]. Mutations in CDKN2A (40%) and CDK4 (3%) are present in familial atypical mole melanoma (FAMMM) syndrome patients. These patients have a 70% lifetime risk of developing melanoma, an increased risk of developing multiple melanomas (30%) and pancreatic cancer (15-20%)[42].

SCC develops from keratinocytes and mainly UV-induced mutations in the p53 gene are important in early events[43]. Chronic sun exposure leads to DNA damage, the accumulation of subsequent mutations causes progression from normal skin, to pre-

cancerous lesion (actinic keratosis or squamous cell carcinoma in situ) and ultimately invasive cancer (SCC) and metastatic SCC. The most important gene mutation in the p53 tumor suppressor gene leads to further accumulation of DNA damage, because in a normal cell p53 causes cell cycle arrest after DNA damage, which removes DNA damage before DNA synthesis and mitosis. Sun-exposed skin contains many p53 mutations (74% compared to 5% in normal skin)[44]. Other signaling pathways that may play a role in SCC development are epidermal growth factor receptor, RAS, Fyn, p16INK4a, c-myc, bcl-2, STAT-3, beta-1 integrin, MMP, Srcasm, Notch (p53), PKC delta, E-cadherin, MMP2, MMP7, MMP12 (ras), and P-cadherin[44]. Major genetic syndromes with increased risks of squamous cell carcinoma are Xeroderma pigmentosum, Oculocutaneous albinism and Epidermodysplasia verruciformis.

The nevoid BCC syndrome (Gorlin Goltz syndrome) is a hereditary syndrome in patients with a mutation in the Patched gene causing multiple BCCs at young age. The patched gene is part of the Hedgehog pathway and in sporadic BCCs also loss-of-function PTCH1 mutations were found[45]. PTCH1 blocks the function of Smoothened (SMO) in the absence of Hedgehog ligands, signaling starts when Hedgehog ligands bind PTCH1 and block its function. The Hedgehog pathway is deregulated in the majority of BCCs by mutations of the signaling repressor PTCH1, but in a minority of tumors a mutation of SMO is present. Systemic and topical Hedgehog inhibitors are currently investigated and are important new therapies for advanced and metastatic BCC, however, the use in the more common less advanced BCC is yet unclear[45].

FOLLOW-UP

The three major reasons for follow-up are the detection of recurrent lesions (and progression of the disease), diagnosis of new malignant lesions and reassurance of the patient[46]. In the Netherlands melanoma patients with stage 1A require, according to the guidelines, one follow-up visit one month after treatment and patient education in order to detect new lesions or recurrence. Patients with stage ≥ 1B are advised to have 5 years of follow-up with a decreasing frequency per year (four follow-up visits in the first year, two in the second year after diagnosis and annually in the next years)[25]. SCC patients require five years of follow-up[23]. According to the BCC guideline, only high risk BCC patients require annual follow-up visits (nevoid BCC syndrome, immunosuppressive medication use and patients with extensive actinic damage), other BCC patients do not require follow-up[22]. In The Netherlands no clear follow-up schemes are available for patients with multiple cutaneous (pre)-malignancies. Internationally, no evidence-based data is available concerning follow-up length and frequency, almost every other country advises lifelong annually follow-up visits[47]. There is also low evidence for skin

self-examination, although education about skin self-examination is widely advised[48]. In the Netherlands, 42% of the medical specialists think less follow-up is needed[49]. However, the frequency of follow-up visits of a large group of melanoma patients (mainly those with lower Breslow thickness) was higher than recommended by the current melanoma guideline in The Netherlands[50], which may be due to patients preferences, and to a lesser extent physicians' preferences.

RISK FACTORS

The most important risk factors associated with melanoma, BCC and SCC and multiple skin cancers are summed in Table 2. One of the most important risk factors of skin cancer is Ultraviolet radiation (UVR). UVR (a potent carcinogen) is subdivided into ultraviolet A (UVA, 315-400 nm), ultraviolet B (UVB, 280-315 nm) and ultraviolet C (UVC, 100-280 nm), around 90-99% of the solar UVR energy that reaches earth's surface is UVA and 1-10% is UVB[51]. Solar skin damage and photoaging are thought to be caused by direct DNA damage (formation of cyclobutane pyrimidine dimers), gene mutations, immunosup-

Table 2. Risk factors of melanoma, squamous cell carcinoma, basal cell carcinoma[53] and multiple skin cancers.

	Melanoma	SCC	BCC	Multiple skin cancers
Exogenous Risk Factors				
Acute UV exposure	++	+	++	++
Intermittent UV exposure	+++	+	++	++
Cumulative UV exposure	+	+++	+	++
Sun-damaged skin (e.g. AK)	+	+++	++	+++
Smoking	n.a.	++	n.a.	n.a.
Ionizing radiation	n.a.	++	+	+
Human papillomavirus	n.a.	+++	+	++
Immunosuppression (e.g. medication, organ transplant)	n.a.	+++	+	+++
Endogenous Risk Factors				
Sex	n.a.	+++	++	+
Age	+	+++	++	++
Pigmentation status (light skin, eyes and hair)	+++	+++	+++	+++
Increasing number of nevi	+++	n.a.	+	++
Atypical nevi	+++	n.a.	+	++
Positive history of skin cancer	+	++	+++	+++
Chronic inflammation	n.a.	+++	+	+
Scarring	n.a.	+++	+	+
Genetics	++	+	+	+++

Abbreviations: 'UV'= ultraviolet; 'AK'= actinic keratosis; 'n.a.' =not applicable.

pression, oxidative stress, and inflammatory responses[51]. UVR leads to mutations of p53 tumor suppressor genes. These genes are involved in DNA repair or the apoptosis of cells with high levels of DNA damage[51]. Skin color, the ozone layer, life style changes (outdoor activities and worsening sunbathing habits), sunburns during childhood, phototherapy and tanning beds are all influencing the individual risk of skin cancer[51].

In 1953, Slaughter et al. described 'field cancerization' in oral epithelium as a regional carcinogenic activity of some kind, in which a preconditioned epithelium has been activated over an area in which multiple cell groups undergo a process of irreversible change toward cancer[52]. Skin cancer and actinic keratosis are strongly associated with sun exposure and therefore field cancerization is an important concept in the occurrence of multiple cutaneous (pre)-malignancies.

AIMS OF THIS THESIS

Important topics like follow-up and early detection of skin cancer remain a subject of debate. In this thesis I describe the burden of multiple cutaneous malignancies and their consequences for patients, doctors and health care systems.

The main questions addressed in this thesis are:

Part I: What are the risks of multiple cutaneous (pre)-malignancies (melanoma, SCC and BCC) in The Netherlands and worldwide (Europe, North America and Australia)?

Part II: What are the trends in incidence of thin melanomas and what is the prevalence of actinic keratosis in The Netherlands?

Part III: What is the conditional relative survival of lymph node negative and positive melanoma patients and patients with multiple melanoma?

Part I: To answer the first research question we performed a large systematic review and meta-analysis to pool current available data concerning risks of a subsequent cutaneous malignancy (including KC or melanoma) in patients with a prior melanoma or KC. The results of this review are presented in chapters 2 and 3. In chapter 4 we used data of the Netherlands Cancer Registry to investigate risks of a second primary melanoma (in situ or invasive) after a first in situ or invasive melanoma and discuss effectiveness and efficiency of screening of second primary melanomas. In chapter 5 we analyzed risks of a subsequent different cutaneous malignancy (melanoma, SCC or BCC) in patients with a prior melanoma or KC. Data from the Eindhoven Cancer Registry includes data on BCC and was used to estimate BCC – melanoma, BCC – SCC, melanoma – BCC and SCC – BCC risks. Data from the Netherlands Cancer Registry includes the Eindhoven Cancer Registry and was used to estimate nationwide melanoma – SCC and SCC – melanoma risks. In chapter 6 we discuss occurrence of exclusive development of keratinocyte carcinoma.

Part II: In chapter 7 we used data of the Netherlands Cancer Registry to investigate time trends of thin melanomas. Incidence rates and estimated annual percentage changes were investigated for in situ melanomas and thin melanomas and trends were compared with thicker melanomas to find signs for overdiagnosis and increased awareness. In chapter 8 we calculated the prevalence of actinic keratosis amongst participants of the Rotterdam Study, a population-based cohort, and also investigated risk factors and detection rates of skin cancer.

Part III: In chapter 9, data of the Netherlands Cancer Registry was used to investigate 5-year conditional relative survival for lymph node negative melanoma patients and 1-year conditional relative survival for lymph node positive and negative patients. In chapter 10, survival of patients with multiple melanoma was investigated using data of the Netherlands Cancer Registry. A Cox proportional hazard model was used to describe the differences between multiple melanoma patients and single primary melanoma patients.

In this thesis different aspects of the epidemiology of multiple cutaneous (pre)-malignancies are described in order to investigate the risks for different skin cancer patients and to provide insight for clinicians and health care management policy makers. I also describe epidemiology of early cutaneous malignancies with data of the Netherlands Cancer Registry and The Rotterdam Study to respectively find signs of overdiagnosis and to emphasize the enormous burden of cutaneous (pre)-malignancies for health care providers. Finally, I will describe the conditional relative survival of melanoma in The Netherlands in order to give a more optimistic message to melanoma survivors than the traditional relative survival rates and the survival of patients with multiple melanoma.

METHODS

In order to answer the research questions described above, I used several methods to estimate pooled risks, risks, incidence, prevalence and survival of skin cancer in the general population. More details are provided in the individual chapters and statistics and/or epidemiology textbooks. In this thesis, I used three types of datasources:

Literature search engines

For the separated systematic review and meta-analysis a comprehensive literature search strategy was performed assisted by a medical librarian of the Erasmus MC University Medical Center, Rotterdam, the Netherlands. PubMed, Embase, Web of Science and the Cochrane library were searched with database-specific search strings. To have insight in grey literature internet search engines (www.google.nl) were also searched. These data were the base of chapters 2 and 3.

Population-based cancer registry data

Population-based cancer registry data of the Netherlands Cancer Registry (NCR) and Eindhoven Cancer Registry (ECR) (www.iknl.nl)were the base of chapters 4, 5, 7, 9 and 10. The nationwide NCR combines data from all comprehensive cancer centers in the Netherlands since 1989. The NCR is based on all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnosis, haematology departments and radiotherapy institutions. Information on patients diagnosed with basal cell carcinoma was obtained from the Eindhoven Cancer Registry, which is the only comprehensive cancer center in the Netherlands that registers BCCs routinely and systematically. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. Population-based cancer registries collect data on all new cases of cancer occurring in a well-defined population (usually a particular geographical region). Main objective of this type of cancer registry is to produce statistics on the occurrence of cancer in a defined population and to provide a framework for assessing and controlling the impact of cancer in the community[54]. Information on the Dutch population size in the past were obtained from Statistics Netherlands (CBS, Centraal Bureau voor de Statistiek, www.cbs.nl).

The Rotterdam Study

The Rotterdam Study is a large prospective population-based cohort study in the Ommoord district in the city of Rotterdam, the Netherlands[55], with recruitment starting in January 1990. Up to 2008, 14,926 subjects aged 45 years or over comprise the Rotterdam Study cohort[56]. Participants were followed for the most common diseases in the elderly. Since 2010 dermatological diseases were examined in the Rotterdam study[56]. Several items were added to the home interview, including questions concerning ultraviolet exposure and history of skin diseases. A full body skin examination by physicians trained in dermatology with a focus on the most common skin diseases including actinic keratosis and cutaneous malignancies at time of examination is assessed in a standardized way[56]. The first dermato-oncological cross-sectional data was the base of chapter 8.

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Part I

Multiple

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CHAPTER 2

Risk of subsequent cutaneous malignancy in patients with prior melanoma: A systematic review and meta-analysis

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J Eur Acad Dermatol Venereol. 2014 Dec 10

ABSTRACT

Melanoma patients are known to be at risk of developing multiple cutaneous (pre-) malignancies, however the exact dimensions of these risks are unknown. In this meta-analysis risks of developing a melanoma, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) after a melanoma were investigated. An extensive systematic literature search was conducted (last performed on January 18, 2012). Studies reporting risks, i.e. proportions, standardized incidence ratios [SIR] and cumulative risks were included. Fifty, of 233 fully read articles, met selection criteria. Two independent reviewers extracted data on study characteristics and risks measurements. Random-effects meta-analyses were used to pool the risk estimates for the three tumour combinations. In melanoma patients, pooled proportions for a subsequent melanoma, BCC or SCC were respectively 3.8% (n=47), 2.8% (n=5) and 1.0% (n=6). The pooled SIRs for a subsequent melanoma, BCC or SCC in melanoma patients were respectively 10.4 (n=12), 4.6 (n=2) and 2.8 (n=2). Mean 20-year cumulative risks of a subsequent melanoma, BCC or SCC in melanoma patients were respectively 5.4% (n=3), 14.0% (n=1) and 4.0% (n=1). Subgroup analyses showed substantial differences in reported risks between continents and study design. In conclusion, a history of a prior melanoma is a strong predictor for development of a subsequent melanoma (approximately 10-fold increased risk) and to a lesser extent BCC or SCC. This information could serve as information for health care systems. Further, secondary prevention seems pivotal in this patient group.

Funding:
The Netherlands Organization for Health Research and Development (ZonMw), project numbers 152001013/VIDI 91711315.

INTRODUCTION

The three most common cutaneous malignancies are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma and their incidence rates are increasing worldwide.[1,2] Skin cancer patients are known to be at risk of developing multiple cutaneous (pre-)malignancies (supplemental Table 1).[3] This is associated with patient morbidity and to a lesser extent mortality, and the management of these malignancies has a high impact on current health care systems and costs. In a recent systematic review and meta-analysis high risk estimates of subsequent skin cancers after a first keratinocyte carcinoma (KC; including BCC and SCC) were found for all tumour combinations, especially for similar subsequent skin cancer (almost 30% for BCC after a BCC).[3]

Melanoma causes most skin cancer related deaths[4], because of its much higher case-fatality rate compared to KC. Fortunately, survival of melanoma has improved, probably because of earlier detection (due to increased skin cancer awareness in the population and early detection by patients and doctors[5]). This improved survival implies that more patients live a long time after diagnosis and therefore likelihood of subsequent (skin) cancers becomes important. Subsequent melanomas appear to be thinner than first melanomas[6], probably due to clinical examinations during follow-up. A structured review in 2005 summarised twelve studies that investigated the risk of a melanoma after a prior melanoma (without systematic search strategy and meta-analysis) to find evidence for melanoma follow-up strategies and stated that more high-quality methodological research is needed as input for follow-up guidelines.[7] Since then, a substantial number of population- and hospital-based studies reported their risk estimates of subsequent melanoma.

Melanoma and KC share many risk factors, such as exposure to ultraviolet radiation, genetic (e.g. ASIP and TYR[8]) and phenotypic characteristics (e.g. hair and skin colour) and indeed, melanoma patients are thought to be at increased risk for both melanoma and KC development.[9-12]

In this systematic review and meta-analysis, the risks of developing a subsequent melanoma or KC were investigated in patients diagnosed with a cutaneous melanoma, stratified for study quality, study design and geographical location. This information could be valuable for patient education, secondary prevention and health care policy makers.

METHODS

We aimed to provide estimates for the development of a subsequent melanoma, BCC or SCC in patients with a history of melanoma. We recently published the risks of these cu-

taneous malignancies amongst KC patients in a separate article.[3] Results were reported according to the PRISMA statement for reporting systematic reviews and meta-analyses of epidemiological studies.[13]

Search strategy

The search strategy is depicted schematically in Supplemental Table 2.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were identical to those of our recent review on patients with a first KC[3], but applied to patients with a first melanoma. In short, if a publication fulfilled the following inclusion criteria it was eligible for inclusion: (1) patients with a previous melanoma were followed over time for the development of a subsequent melanoma, BCC or SCC and an associated proportion, standardized incidence ratio (SIR) or cumulative risk (CR) was provided; (2) more than 80% of the skin cancer cases were histopathologically confirmed; (3) findings reported in English.

Of the above mentioned eligible risk estimates, the proportion was the most frequently reported in the literature. However, this estimate is not very informative as it increases with follow-up time, but does not correct for it, does not account for the competing risk 'death' and does not compare to the risk in the non-melanoma population, unlike the preferable CR and SIR.

The following exclusion criteria were used: (1) specific patient populations who were at extreme risk of developing cutaneous malignancies (e.g. transplant patients or genodermatoses); (2) more than 10% of the first or subsequent cutaneous malignancies were recurrences or no adequate case definition was made (e.g. no distinction between recurrences and first or subsequent cutaneous malignancies); (3) animal studies; (4) review, editorial, meta-analysis, consensus, guideline, case-reports or case – series; (5) only reporting cutaneous malignancies on specific anatomical sites.

Study selection

The following three tumour combinations of interest were investigated: melanoma after melanoma, BCC after melanoma and SCC after melanoma (see *part II* of Figure 1). Some included studies reported separate observations for multiple tumour combinations. If identical populations were described in several publications within the same or overlapping time period, these publications were compared and the study with the most detailed results was included.

Data extraction

The study characteristics are listed in Supplemental Table 1.

Quality assessment

The study quality was assessed by using adapted criteria (Supplemental Table 3) from the Newcastle-Ottawa quality assessment scale (NOS) which is a quality assessment tool for cohort and case-control studies in systematic reviews and meta-analyses.[14] The NOS is divided within three grouping items: selection (4 points), comparability (2 points) and outcome (3 points). The maximum score of an article was 9 points. The risk of bias was considered moderate or low when the overall sum was 5 points or higher.[15]

Statistical methods

Despite its disadvantages compared to SIR and CR, the primary outcome of this meta-analysis was the proportion of melanoma patients that developed a subsequent cutaneous malignancy (i.e., melanoma, BCC or SCC) because it was by far the most commonly used estimate. This proportion was calculated by dividing the number of patients with a subsequent skin cancer by the total number of followed patients. The second, more informative, outcome of interest was SIR, calculated as the observed number of patients that developed a subsequent cutaneous malignancy divided by the expected number of patients in the general population (i.e. background incidence). Thirdly, the CR was calculated by dividing the number of patients that developed a subsequent cutaneous malignancy by the total number of patients alive after a certain time period.

Pooled estimates for proportion and SIR with 95% confidence intervals (95%CI) were calculated with a random effects model as proposed by DerSimonian and Laird because of high study heterogeneity (I^2 index>75%).[16,17] In this model, the inverse of standard errors of proportion and SIR from the individual studies combined with the between study variation were used as weights. Only a limited number of studies provided a CR and most of them provided a 5–year or 10-year CR. Moreover, CI and life tables were often lacking, making it impossible to calculate a pooled CR. However, to provide an overview of the available CR data, the available 1-year, 5–year, 10-year, 15-year and 20-year cumulative risks were averaged.

Subgroup analyses (only performed when number of separate observations per tumour combination ≥5) and sensitivity analyses were performed to understand the 'robustness' of the data and to find possible sources for study heterogeneity.[18] In the subgroup analyses the following study characteristics were compared, overall NOS score <5 versus ≥5, population- versus hospital-based, in- versus exclusion of in situ cutaneous malignancies, studies that explicitly stated to follow patients with a 'first' melanoma versus studies without this statement (i.e., unknown if the patients under study were 'new' skin cancer patients or not). Stratification by study continent (i.e., Australia, North America and Europe) was also performed. Publication bias was statistically assessed by funnel plots and the Eggers' test (Supplemental Figure 1).[19]

All statistical analyses were performed using the software package Comprehensive meta-analysis (version 2.2) and SPSS statistical software (version 18 and 21 for Windows, SPCC Inc, Chicago, Illinois).

RESULTS

The literature search identified 10,147 articles of which 233 were found potentially eligible based on title or abstract. Of the 233 fully read articles, 50 were eligible in the prior melanoma analysis (Figure 1). In these 50 articles (Supplemental Table 1), a total of 61 separate observations (i.e., a part of the articles contained information on multiple tumour combinations) were reported for the three eligible tumour combinations. Of these 61 separate observations, 48 had melanoma as subsequent tumour, 7 BCC, and 6 SCC. The 61 observations in this meta-analysis included 55 cohort and 6 case – control studies. Almost thirty percent of the articles were population-based (n=16), of which 13 used cancer registry data. In total, 9 observations had a prospective, while 52 had a retrospective study design. Of 55 observations the full text was available, whereas for 6 only abstracts could be retrieved.[20-25] Sixteen countries were represented in the studies, corresponding to three continents (i.e. Australia, North America and Europe). Of the 55 full articles, 70% of the observations were appraised with a high quality score (≥5 NOS score).

Pooled proportion

In Figure 2 A-C, the pooled proportions for respectively a subsequent melanoma, BCC or SCC after a melanoma are shown; 3.8% (95%CI 3.3-4.4%; n=47), 2.8% (2.0-3.7%; n=5) and 1.0% (0.6–1.8%; n=6).

Pooled estimates within the subgroup analyses showed higher pooled proportions in the melanoma after melanoma tumour combination for hospital based studies versus population based studies (respectively 4.3% versus 2.6% [Table 1]). Further, studies including in situ melanomas versus excluding in situ melanomas showed a higher proportion (respectively 4.9% versus 3.2%), as well as Australian studies in comparison with European and USA studies (respectively 5.6% versus 3.5% and 3.5% [Table 1]).

After stratifying for sex, the pooled proportions for subsequent skin tumours after a melanoma were higher for men compared to women (men: melanoma 3.9% [95% CI 2.9 – 5.2], n=15; BCC 4.9% [95% CI 3.7 – 6.4], n=2; SCC 1.2% [95% CI 0.3 – 4.7], n=2; and, women: melanoma 3.3% [95% CI 2.5 – 4.4], n=15, BCC 2.7% [95% CI 1.5-4.7], n=2, SCC (0.6% [95% CI 0.1 – 2.8], n=2).

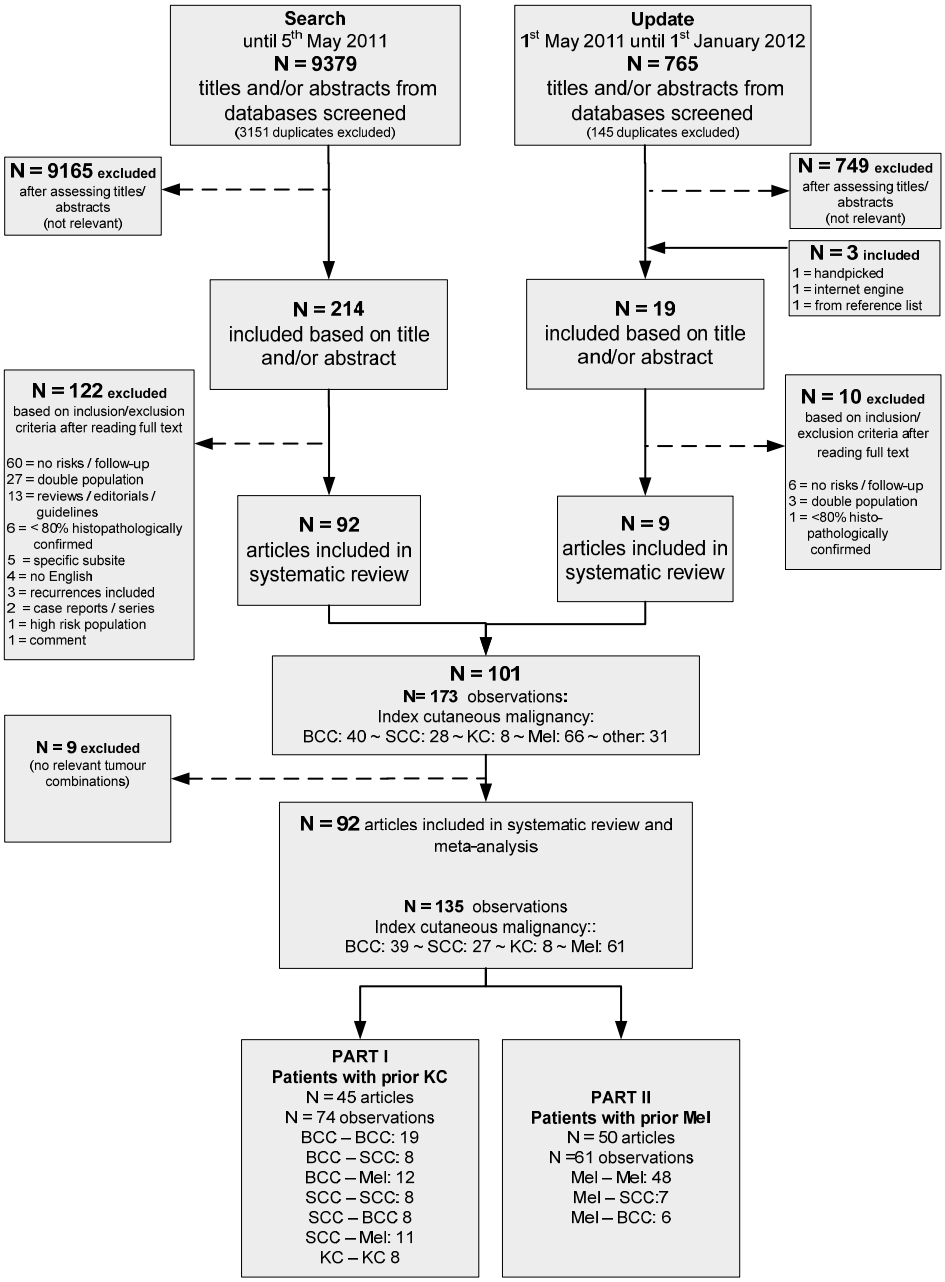
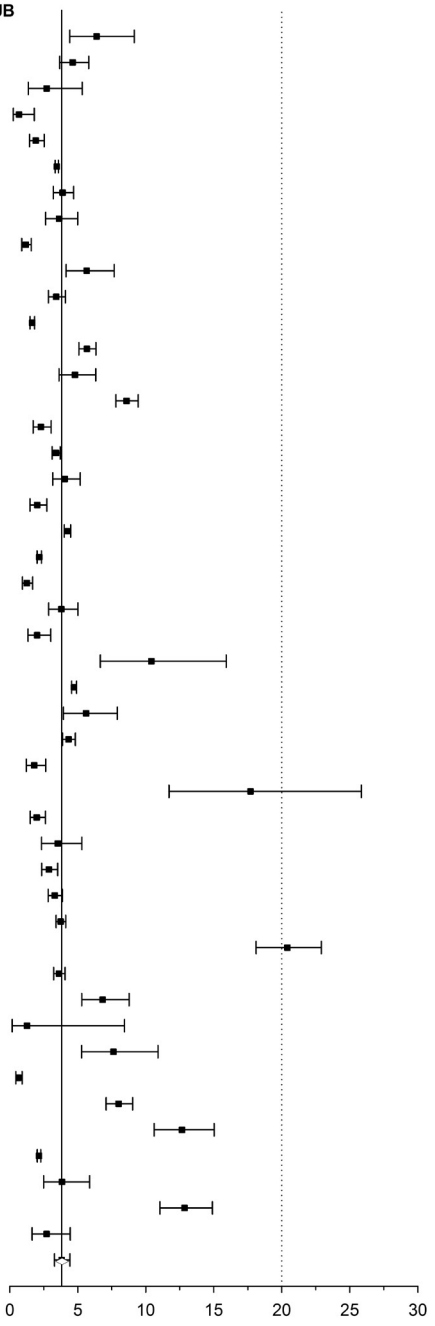


Figure 1. Selection process of included articles

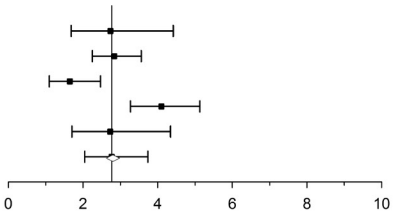
A

Study	Year	Proportion (%)	95% LB	95% UB
Ariyan	1995	6.38	4.41	9.15
Beardmore	1977	4.62	3.67	5.80
Bellet	1974	2.71	1.36	5.33
Bhatia	1999	0.68	0.26	1.81
Bower	2010	1.92	1.45	2.53
Bradford	2010	3.46	3.34	3.58
Brobeil	1997	3.88	3.21	4.70
Buljan	2010	3.63	2.63	5.00
Burden	1994	1.18	0.88	1.57
De Giorgi	2011	5.65	4.14	7.68
DiFronzo	1999	3.41	2.85	4.09
Dong	2001	1.65	1.49	1.82
Doubrovsky	2003	5.68	5.08	6.34
Echeverria	2010	4.79	3.62	6.32
Ferrone	2005	8.59	7.80	9.44
Garbe	2003	2.29	1.72	3.05
Giles	1995	3.40	3.12	3.71
Johnson	1998	4.05	3.16	5.18
Kang	1992	2.02	1.49	2.73
Karahalios	2009	4.24	4.01	4.48
Leiter	2012	2.17	2.01	2.33
Levi	2005	1.25	0.93	1.68
Manganoni	2007	3.79	2.86	5.01
Marghoob	1996	2.01	1.34	3.01
Marghoob	1996	10.40	6.65	15.91
Mcaul	2008	4.73	4.55	4.91
Nashan	2003	5.61	3.95	7.91
Osterlind	1985	4.33	3.88	4.82
Ray	1985	1.80	1.22	2.65
Salava	2010	17.70	11.71	25.85
Savoia	1998	1.98	1.50	2.62
Schallreuter	1993	3.53	2.34	5.30
Scheibner	1982	2.88	2.35	3.52
Schmid-Wendtner	2001	3.31	2.83	3.86
Schoellhammer	2009	3.75	3.41	4.12
Siskind	2011	20.41	18.11	22.91
Slingluff	1993	3.62	3.23	4.06
Stam-Posthuma	2001	6.83	5.29	8.77
Stang	2007	1.27	0.18	8.44
Titus-Ernstoff	2006	7.63	5.28	10.89
Tucker	1985	0.64	0.45	0.91
Turner	2011	8.01	7.09	9.03
Uliasz	2007	12.66	10.61	15.03
van der Leest	2012	2.15	2.02	2.28
Veronesi	1976	3.84	2.49	5.87
Wendt	2010	12.84	11.04	14.90
Wolff	2000	2.71	1.64	4.44
Pooled proportion		**3.82**	**3.29**	**4.42**



B

Study	Year	Proportion (%)	95% LB	95% UB
Bhatia	1999	2.74	1.68	4.42
Bower	2010	2.83	2.25	3.56
Kroumpouzos	2000	1.65	1.10	2.47
Levi	1997	4.10	3.27	5.13
Schallreuter	1993	2.73	1.70	4.35
Pooled proportion		**2.77**	**2.05**	**3.74**



C

Study	Year	Proportion (%)	95% LB	95% UB
Bhatia	1999	0.50	0.24	1.05
Bower	2010	1.24	0.87	1.75
Helm	1996	3.41	1.95	5.91
Kroumpouzos	2000	1.35	0.91	2.00
Levi	1997	0.51	0.17	1.58
Schallreuter	1993	0.16	0.02	1.13
Pooled proportion		**1.04**	**0.58**	**1.84**

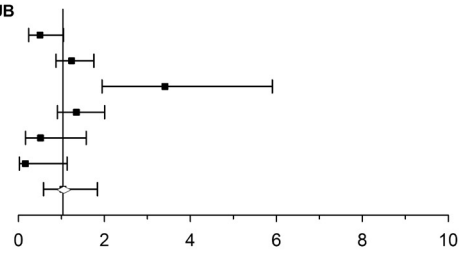


Figure 2. Risk (%) of subsequent cutaneous malignancy in patients with prior melanoma
A Melanoma after melanoma
B Basal cell carcinoma (BCC) after melanoma
C Squamous cell carcinoma (SCC) after melanoma

Pooled SIR

Pooled SIRs, Figure 3 A-C, which compare the observed incidence to the expected incidence in the general population, showed that patients with a melanoma had a 10-fold (SIR 10.4 [8.5–12.3; n=12]) increased risk of a subsequent melanoma compared to the general population. The pooled SIRs of BCC after melanoma was 4.6 (95% CI 3.9-5.4; n=2) and SCC after melanoma 2.8 (95% CI 1.9-3.7; n=2) (Table 2).

Subgroup analyses were only performed for the melanoma after melanoma tumour combination ($n \geq 5$). Pooled estimates within the subgroup analyses showed higher pooled SIRs for hospital-based studies versus population-based studies (respectively 17.8 versus 7.9, Table 2) and studies including in situ melanomas versus excluding in situ melanoma (respectively 21.3 versus 7.8) and first tumour no versus first tumour yes (respectively 84.0 versus 10.6). The other subgroups had overlapping confidence intervals (Table 2).

Mean cumulative risks

Supplemental Table 4 describes mean CR of a subsequent melanoma, BCC or SCC for 1, 5, 10, 15 and 20 years after the first primary melanoma. The highest mean CR was found after 20 years in the BCC after melanoma group with 14%, followed by melanoma (5.4%) and SCC (4.0%).

Table 1. Overview of pooled estimates of proportion with subgroup analyses for all observations

	Melanoma after Melanoma (%, 95% CI)	BCC after melanoma (%, 95% CI)	SCC after melanoma (%, 95% CI)
n studies	47	5	6
Pooled estimate proportion	3.8 (3.3-4.4)	2.8 (2.0-3.7)	1.0 (0.6-1.8)
n studies	13	1	1
NOS ≥5	3.8 (2.9-4.9)	4.1 (2.7-6.1)	1.3 (0.3-6.5)
n studies	34	4	5
NOS <5	3.8 (3.2-4.6)	2.5 (1.9-3.2)	0.9 (0.4-2.0)
n studies	11	1	1
Population-based	2.6 (1.9-3.5)	4.1 (2.7-6.1)	1.3 (0.3-6.5)
n studies	36	4	5
Hospital-based	4.3 (3.7-5.2)	2.5 (1.9-3.2)	0.9 (0.4-2.0)
n studies	14	3	3
***In situ* not included**	3.2 (2.5-4.2)	2.8 (1.8-4.3)	1.0 (0.5-1.9)
n studies	20	1	1
***In situ* included**	4.9 (3.9-6.0)	2.7 (1.1-6.3)	0.2 (0.0-1.5)
n studies	13	1	2
***In situ* included unknown**	3.1 (2.3-4.1)	2.7 (1.1-6.4)	1.7 (0.7-4.2)
n studies	26	1	1
First tumour yes	4.0 (3.3-4.9)	4.1 (2.7-6.1)	1.3 (0.4-4.5)
n studies	8	0	1
First tumour no	4.4 (3.0-6.4)	NA	3.4 (0.9-11.6)
n studies	13	4	4
First tumour unknown	3.1 (2.3-4.2)	2.5 (1.9-3.2)	0.6 (0.3-1.3)
n studies	21	2	2
Europe	3.5 (2.8-4.3)	3.5 (2.4-5.2)	0.7 (0.2-2.8)
n studies	18	3	4
USA	3.5 (2.8-4.5)	2.4 (1.7-3.3)	1.1 (0.5-2.6)
n studies	8	0	0
Australia	5.6 (4.0-7.8)	NA	NA

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; NA, not applicable, NOS, Newcastle – Ottawa scale; SCC, squamous cell carcinoma; USA, United States of America.

Sensitivity analyses

Five outliers were observed in the pooled proportion forest plot of melanoma after melanoma leading to substantial variation of proportions ranging from 0.64 to 20.4%. Three of these outliers included studies with high risk patients: Marghoob et al.[26] analysed a cohort of patients of which 27.7% had a classical atypical mole syndrome,

Table 2. Overview of pooled estimates of standardised incidence ratios with subgroup analyses for all observations

	Melanoma after Melanoma (SIR, 95% CI)	BCC after melanoma (SIR, 95% CI)*	SCC after melanoma (SIR, 95% CI)*
n studies	12	2	2
Pooled estimate proportion	10.4 (8.5-12.3)	4.6 (3.9-5.4)	2.8 (1.9-3.7)
n studies	7		
NOS ≥5	8.7 (6.3-11.0)		
n studies	5		
NOS <5	14.1 (10.7-17.5)		
n studies	7		
Population-based	7.9 (5.7-10.1)		
n studies	5		
Hospital-based	17.8 (14.1-21.7)		
n studies	6		
***In situ* not included**	7.8 (5.4-10.1)		
n studies	3		
***In situ* included**	21.3 (16.5-26.0)		
n studies	3		
***In situ* included unknown**	10.1 (5.6-14.6)		
n studies	8		
First tumour yes	10.6 (8.5-12.8)		
n studies	1		
First tumour no	84.0 (64.3-103.7)		
n studies	3		
First tumour unknown	7.1 (3.7-10.6)		
n studies	6		
Europe	14.0 (9.5-18.6)		
n studies	5		
USA	11.8 (6.7-16.9)		
n studies	1		
Australia	7.3 (0.0-17.4)		

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; KSC, keratinocytic skin cancer; n, number; NA, not applicable; NOS, Newcastle – Ottawa scale; SCC, squamous cell carcinoma; SIR, standardised incidence ratio; USA, United States of America.
*Too low number for subanalyses.

Salava et al.[21] described patients with more than 100 naevi or more than 5 clinical atypical naevi and Siskind et al.[27] included patients with high familial melanoma risk. The other two outliers were relatively small hospital-based studies, which could have inflated the observed proportions.[25,28] After excluding these five outliers in a sensitivity

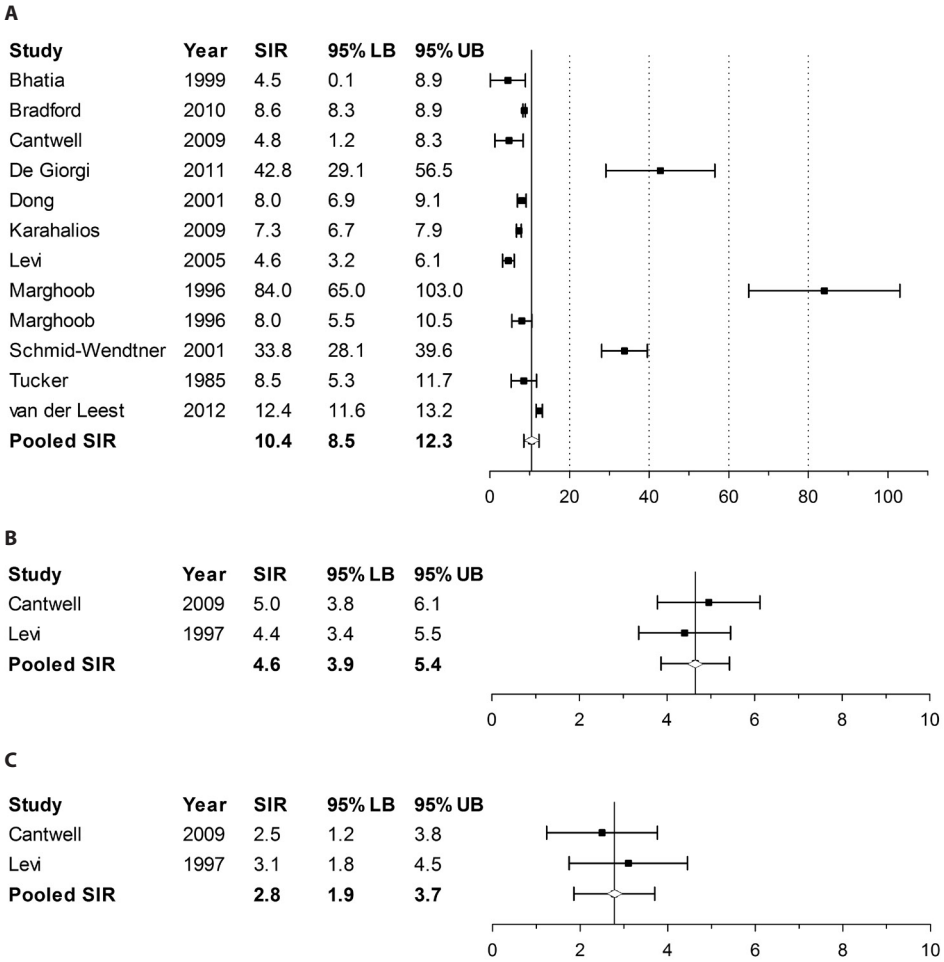


Figure 3. Standardised incidence ratio (SIR) of subsequent cutaneous malignancy in patients with prior melanoma

A Melanoma after melanoma

B Basal cell carcinoma (BCC) after melanoma

C Squamous cell carcinoma (SCC) after melanoma

analysis the pooled proportion of developing a second melanoma decreased from 3.8 to 3.3% (95%CI 2.9-3.7). In the other tumour combinations only one outlier was found in the SCC after melanoma group, however this was the smallest study (n=352) with a relatively small weight in the pooled proportion.[29] In the SIR forest plots, three outliers were present in the melanoma after melanoma group. In these three studies, hospital based incidences were divided by cancer registry based expected incidences to roughly estimate the SIRs.[26,30,31] After excluding these studies in a sensitivity analysis, the pooled SIR decreased from 10.4 to 7.7 (95%CI 6.3-9.2).

DISCUSSION

This systematic review and meta-analysis emphasizes that a melanoma history is among the strongest risk factors of developing a subsequent primary melanoma and to a lesser extent subsequent BCC or SCC. The highest SIR was found for melanoma after melanoma, implying that despite shared risk factors, there are carcinogenetic differences between the three cutaneous malignancies.[3]

However, the increased risk of developing a subsequent BCC or SCC after a first melanoma suggests a partially common aetiology of UV-induced field cancerization and genetic predisposition among these three types of skin cancer.[8,32] The risk was a twofold higher for people to develop a subsequent BCC than a SCC after their melanoma. An explanation for this phenomenon could be the fact that BCC and melanoma share sunburn and intermittent UV exposure as a common risk factor, while the development of SCC is associated with cumulative UV exposure.[10,33,34] Genetically, ASIP and TYR pigmentation variants have been associated with both cutaneous melanoma and BCC.[8] Unfortunately, it was not possible to stratify for histological subtype of melanoma. Most probably the increased risk of developing a SCC after a melanoma may be driven by the lentigo maligna melanoma subtype, which is most often located on the face and also associated with chronic and high levels of UV – exposure.

A positive melanoma history is related to a tenfold increased risk to develop a subsequent melanoma. This high risk is almost comparable to the risk of patients that have hundreds or more common naevi or those that have more than five atypical moles (pooled RR 6.9 or 6.4 respectively) to develop a melanoma[35], and is much higher than other known melanoma risk factors such as increased UV exposure, sun bed use, family history of melanoma, light skin and hair colour, pre-malignant and skin cancer lesions and actinic damage indicators (pooled elevated relative risks between 1.3 – 4.3) emphasizing the need for secondary prevention in this patient population.[10,11] Therefore, melanoma patients need to be informed about their persistent future risk, motivated to perform self-examinations and, if feasible, have annual total body skin examinations for at least five years or even lifelong (duration of follow-up remains debatable and differs across countries) by trained physicians or nurse practitioners in order to detect second melanomas early.

Subgroup analyses

Incidence rates of a primary skin cancer depend on geographic latitude.[10,36] Stratification for continent showed, as expected by decreasing UV-levels, that effect sizes of developing subsequent skin cancers after a first melanoma were the highest for Australia, followed by North America and Europe. This is in accordance with the incidence

rates of a first skin cancer for these regions at different geographic latitudes. Therefore, the pooled risk estimates of all studies combined should be interpreted with caution because they are biased by geographic location limiting the generalizability of the results. Australian studies tended to show lower pooled SIRs compared to European and USA studies (respectively 7.3 versus 14.0 and 11.8), which may be explained by the high background incidence of melanoma in Australia (Table 2). Unfortunately, only a limited number of countries (n= 16) and continents (n= 3) were available and the number of studies in some geographic areas was low. Although we performed subgroup analyses by continents, differences in the distribution of people's characteristics such as pigmentation status (i.e. eye-, hair- and skin colour) were not accounted for further affecting the generalizability. No pooled estimates could be calculated for Africa, Asia, South-America and inhabitants of the Middle-East, but considering the darker pigmentation status of these inhabitants, cutaneous malignancies are a smaller public health issue in these regions.[37]

Consequences and follow-up

The US preventative task force recommended a case-finding approach in the screening of skin cancer.[38] Although total body skin examinations of all patients visiting a physician may not be feasible in clinical practice, it should be mandatory in patients with a history of skin cancer (i.e. melanoma, BCC and SCC) because of their extremely high risk for subsequent malignancies.[3] Other important reasons of following patients with cutaneous malignancies are for psychosocial support, (early) detection of a local recurrence and progression of SCC and melanoma to the draining lymph nodes and visceral organs.[39] Frequency and duration of follow-up of skin cancer patients remains controversial, but purely from the perspective of developing subsequent cutaneous malignancies lifelong follow-up seems desirable. However, lifelong follow-up visits will also increase the number of subsequent cutaneous malignancies by possible 'overdiagnosis', as is hypothesized for the thinner subsequent melanomas.[40] Besides, health care systems differ across countries and increased follow-up might induce a partial switch of skin cancer care to general practitioners and psychological effects of follow-up differ in patients.[39,41]

Strengths and limitations

This is the largest systematic review and meta-analysis available on risk of subsequent skin cancer after a melanoma. To ensure high quality reporting, the PRISMA guidelines were used.[13] The pooled risk estimates presented for a BCC after a melanoma are probably underestimated, because some BCCs may be diagnosed clinically without histological confirmation.[42] This problem is almost non-existent for melanoma and SCC, because these cutaneous malignancies have a higher metastatic potential than BCC

and are usually surgically treated and histologically confirmed. A recent European study observed that only 0.7 – 24.1% of the subsequent BCCs in patients with a prior BCC were clinically diagnosed, indicating that the degree of underestimation of our data is relatively limited, but country-specific.[42] The risk estimate proportion was the most frequently reported estimate in the literature describing risks of subsequent cutaneous malignancies, but has the disadvantage that it does not control for the background incidence in the general population and it is not time-specific nor does it account for the competing risk 'death'. Therefore, we strongly recommend the use of relative risks (SIR) and CR in future subsequent (cutaneous) malignancy research.[43] Unfortunately, the number of studies providing SIRs of the tumour combinations of interest was low, which may be a KC specific problem. Most cancer registries do not register BCCs and those that do usually only reliably report the first histologically confirmed BCCs only. Therefore, the risk of a subsequent BCC or SCC was primarily based on smaller studies that may have underestimated the pooled proportions by shorter follow-up. Also, the younger age at inclusion of melanoma patients (on average 50 years) together with limited follow-up time could have influenced the pooled BCC or SCC risk negatively, because these tumours mainly appear at older ages. Further, only a small group of studies presented CRs in their results and therefore these averaged CRs should be interpreted with caution.

Publication bias due to negative findings is likely to be minimal because the risk estimates of developing a subsequent cutaneous malignancy are probably increased in all studies, as illustrated in this review, minimizing negative findings and thus publication bias.[44] This was supported by symmetrical funnel plots and non-significant Egger's tests showing no signs of publication bias (Supplemental Figure 1). The systematic literature search was done by a medical librarian using a search string and included congress abstracts and monographs (i.e., 'grey literature').[45] However, language bias may have had an effect because only studies reported in English were eligible. To control for multiple publication bias, only the study that presented the most extensive results or had the longest follow-up was included.

CONCLUSION

A history of a prior melanoma is among the strongest predictors for developing a subsequent melanoma and to a lesser extent BCC or SCC. Therefore, secondary prevention is pivotal in patients with a prior melanoma and patients should be well informed about future risk of subsequent skin cancers and sun protection.

ACKNOWLEDGEMENTS

We would like to thank Louis Volkers (medical librarian) from the Erasmus MC University Medical Center Rotterdam, the Netherlands for assistance in developing an accurate search strategy and Emmilia Dowlatshahi for her help with statistical analyses.

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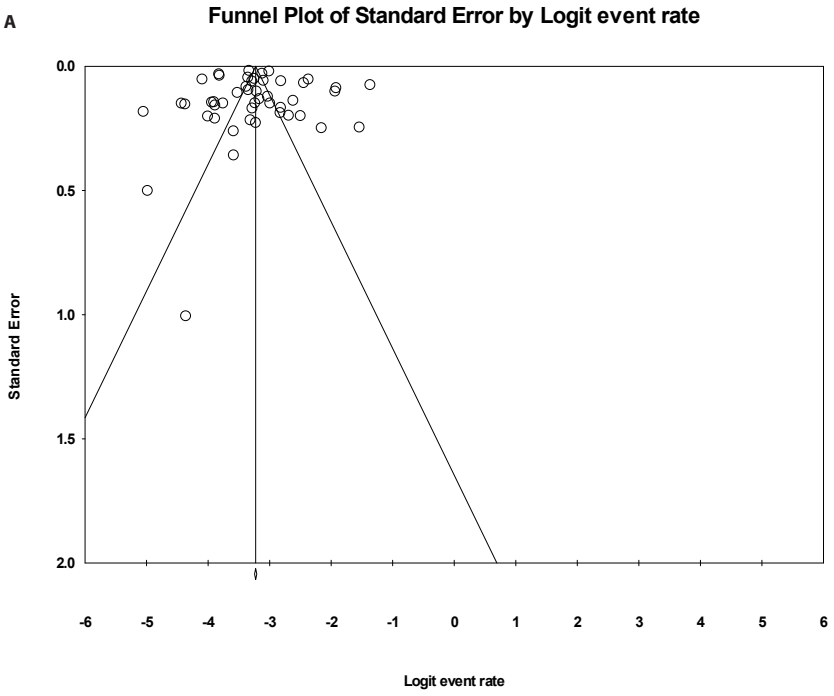
SUPPLEMENTAL TABLES AND FIGURES

A



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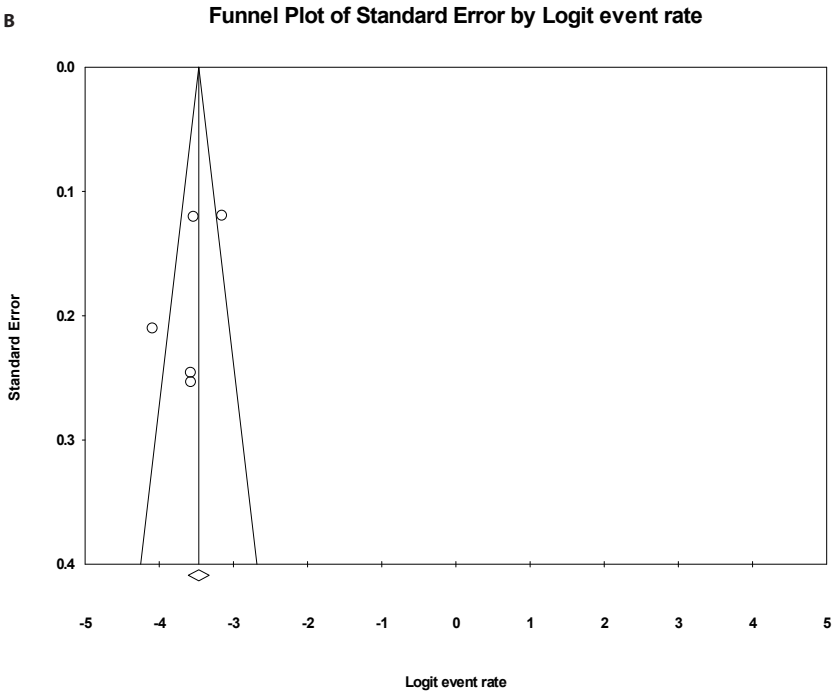

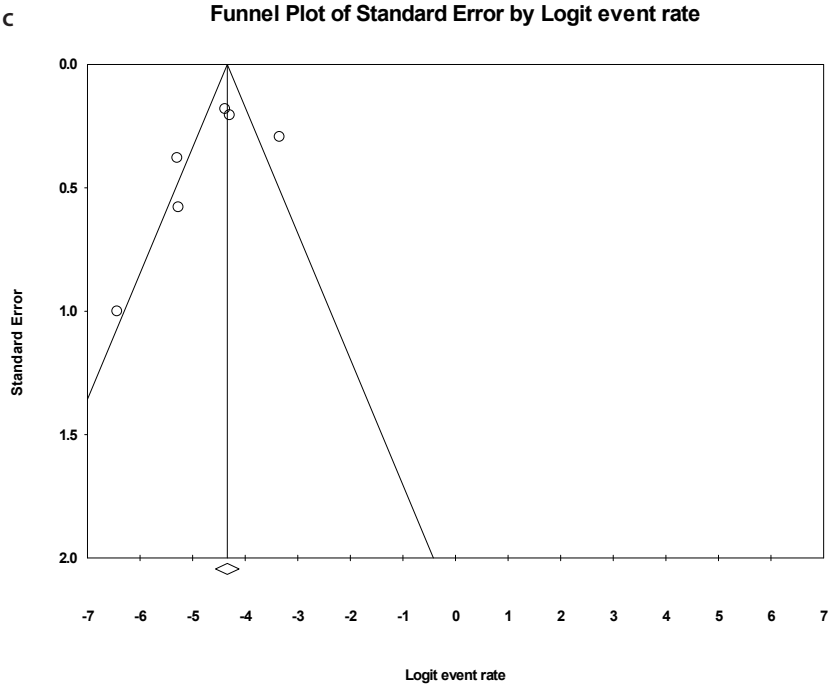

Supplemental Figure 1. Funnel plot with Egger's test of studies reporting a proportion (%)

A Melanoma after melanoma (p-value 0.76)

B Basal cell carcinoma (BCC) after melanoma (p-value 0.30)

C Squamous cell carcinoma (SCC) after melanoma (p-value 0.30)

Supplemental Table 1. Study characteristics

A. Melanoma after melanoma (n=48)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
[1]	1995	USA	1983 - 1993	Retrospective	Cohort	No	H		423	6.4	52	3.3		0	1	1	2
[2]	1977	Australia	1963 - 1969	Prospective	Cohort	No	H		1,514	4.6				1	1	1	3
[3]	1974	USA		Retrospective	Cohort	No	H		295	2.7	47			0	1	1	2
[4]	1999	USA	1952 - 1996	Retrospective	Cohort	No	H		585	0.7	43		4,390	0	2	1	3
[5]	2010	USA	1997 - 2003	Retrospective	Cohort	No	H	Aged > 18 yrs or < 70 yrs Breslow > 1 mm	2,506	1.9	50	5.5	12,805	0	2	1	3
[6]	2010	USA	1973 - 2006	Retrospective	Cohort	Yes	P		89,515	3.5	54	9.2	822,241	3	2	2	7
[7]	1997	USA	8 year period	Retrospective	Cohort	No	H		2,600	4.3	46			1	1	1	3
[8]	2010	Croatie	2002 - 2008	Retrospective	Cohort	No	H		991	3.6	54			1	0	0	1
[9]	1994	Scotland	1979 - 1991	Retrospective	Cohort	No	P		3,818	1.2				3	0	1	4
[10]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P				56	4.0		4	1	3	8
[11]	2011	Italie	1988 - 2009	Retrospective	Cohort	Partly	H		672	5.7		5.0		1	2	2	5
[12]	1999	USA	1971 - 1998	Retrospective	Cohort	No	H	AJCC Stage I and II	3,310	3.4		9.7	34,682	1	2	2	5
[13]	2001	Sweden	1958 - 1996	Retrospective	Cohort	Yes	P		22,164	1.6	53			4	2	1	7
[14]	2003	Australia	1983 - 1999	Retrospective	Cohort	No	H	AJCC Stage I and II (but in situ excluded)	5,250	5.7	54	5.1		0	1	2	3

Supplemental Table 1. (continued)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S C O T
[15]	2010	Spain	1990 - 2009	Retrospective	Cohort	No	H		981	4.8	54	3.8		1 0 2 3
[16]	2005	USA	1996 - 2002	Prospective	Cohort	No	H		4,484	8.6	55	2.3	10,957	1 2 0 3
[17]	2003	Germany	1996 - 1998	Prospective	Cohort	No	H		2,008	2.3	54	2.0		0 0 1 1
[18]	1995	Australia	1985 - 1991	Retrospective	Cohort	Yes	P		14,590	3.4	55	7.0		3 2 1 6
[19]	1998	USA	1990 - 1995	Retrospective	Cohort	No	H		1,482	4.0	51	8.0		0 0 1 1
[20]	1992	USA	1965 - 1989	Retrospective	Cohort	No	H		2,032	2.0	49	6.9		0 0 1 1
[21]	2009	Australia	1982 - 2005	Retrospective	Cohort	Yes	P		28,252	4.2	56	7.7	216,563	4 2 2 8
[22]	2012	Germany/Austria/Switzerland	1976 - 2007	Retrospective	Cohort	No	H	AJCC stages 1.2.3	33,384	2.3	54	4.1		3 0 2 5
[23]	2005	Switzerland	1974 - 2003	Retrospective	Cohort	Yes	P		3,439	1.3			24,930	4 2 2 8
[24]	2007	Italy	1996 - 2006	Retrospective	Cohort	No	H		1,240	3.8	46			0 1 1 2
[25]	1996	USA	-	Retrospective	Cohort	No	H	Whites	1,142	2.0				0 1 2 3
[25]	1996	USA	-	Retrospective	Cohort	No	H	Whites	173	10.0	49	6.5		0 1 2 3
[26]	2008	Australia	1982 - 2003	Retrospective	Cohort	Yes	P		52,997	4.7	55		361,588	4 2 2 8
[27]	2003	Germany	-	Retrospective	Cohort	No	H		535	5.6	52	5.6		0 0 1 1
[28]	1985	Denmark	1943 - 1980	Retrospective	Cohort	No	P		7,211	4.3	54	6.1	42,994	4 2 2 8
[29]	1985	USA	26 year period	Retrospective	Cohort	No	H		1,390	1.8				0 0 1 1
[30]	2010	Finland	-	Prospective	Cohort	No	H		113	17.7		5.0		0 0 0 0
[31]	1998	Italy	1974 - 1997	Retrospective	Cohort	No	H		2,470	2.0	54	12.0		0 0 2 2
[32]	1993	Germany	1989 - 1989	Prospective	Case-control	No	H		623	3.5	53			0 1 1 2

Supplemental Table 1. (continued)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S C O T
[33]	1982	Australia	1951 - 1980	Retrospective	Cohort	No	H		3,128	2.9	45			1 0 1 2
[34]	2001	Germany	1977 - 1992	Prospective	Cohort	No	H		4,597	3.3		2.8		1 1 1 3
[35]	2009	USA	1971 -	Retrospective	Cohort	No	H	stage I and II melanoma	10,968	3.7				1 0 1 2
[36]	2011	Australia	1982 - 2009	Retrospective	Cohort	No	H	overs-ampled familial melanoma risk in patients	1,083	20.4	46	16.5		2 1 2 5
[37]	1993	USA	1972 -	Prospective	Cohort	No	H		7,816	3.6				0 2 1 3
[38]	2001	Netherlands	1983 - 1995	Retrospective	Cohort	No	H		820	6.8	38			1 0 1 2
[39]	2007	Germany	1998 - 2003	Retrospective	Cohort	No	H		79	1.3	47			1 2 1 4
[40]	2006	USA	2 year period	Retrospective	Cohort	No	P	20 - 69 year. with working TF. speak English	354	8.0	53			2 2 1 5
[41]	1985	USA	1935 - 1982	Retrospective	Cohort	Yes	P		4,693	0.6	52	5.9		1 1 1 3
[42]	2011	Australia	1985 - 2009	Retrospective	Cohort	No	H	AJCC stage I or II	2,998	8.0	55	2.7		1 2 1 4
[43]	2007	USA	2000 - 2003	Retrospective	Cohort	No	H	in situ/ AJCC stage I and II	877	12.7				1 0 1 2

Supplemental Table 1. (continued)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
[44]	2012	Netherlands	1989 - 2008	Retrospective	Cohort	Yes	P		46,700	2.2	52	4.9	301,758	4	2	2	8
[45]	1976	Italy	1967 - 1974	Retrospective	Cohort	No	H		521	3.8			1,263.1	0	2	0	2
[46]	2010	Austria	2008 - 2010	Retrospective	Cohort	No	H		1,160	12.8	53			0	0	0	0
[47]	2000	Germany	1966 - 1999	Retrospective	Cohort	No	H		554	2.7	54	5.6	3,111.5	1	1	2	4

B Basal cell carcinoma (BCC) after melanoma (n=6)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Sub-group	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
[4]	1999	USA	1952 - 1996	Retrospective	Cohort	No	H		585	2.7	43		4,390	0	2	1	3
[5]	2010	USA	1997 - 2003	Retrospective	Cohort	No	H	Aged > 18 yrs or < 70 yrs Breslow > 1 mm	2,506	2.8		5.5	12,805	0	2	1	3
[10]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P				56	4.0		4	1	3	8
[48]	2000	USA	1977 - 1978	Retrospective	Case-control	No	H		1,396	1.7	50	4.0		1	2	0	3
[49]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P		1,780	4.1	59		9,582	4	2	2	8
[32]	1993	Germany	1989 - 1989	Prospective	Case-control	No	H		623	2.7	53			0	1	1	2

C. Squamous cell carcinoma (SCC) after melanoma (n=7)

First author	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% sub-sequent tumour	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S C O T
[4]	1999	USA	1952 - 1996	Retrospective	Cohort	No	H		585	0.5	43		4,390	0 2 1 3
[5]	2010	USA	1997 - 2003	Retrospective	Cohort	No	H	Aged > 18 yrs or < 70 yrs Breslow > 1 mm	2,506	1.2		5.5	12,805	0 2 1 3
[10]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P				56	4.0		4 1 3 8
[50]	1996	USA	1980 - 1990	Retrospective	Case-control	No	H		352	3.4				0 2 1 3
[48]	2000	USA	1977 - 1978	Retrospective	Case-control	No	H		1,396	0.5	50	4.0		1 2 0 3
[49]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P		1,780	1.3	59		9,582	4 2 2 8
[32]	1993	Germany	1989 - 1989	Prospective	Case-control	No	H		623	0.2	53			0 1 1 2

Abbreviations: BCC. basal cell carcinoma; KC. keratinocyte carcinoma; Mel; melanoma; N. number; SCC. squamous cell carcinoma

Supplemental Table 2. Search strategy and strings

Search strategy

Database	Search string[a]	Number of articles (first search performed on May 5th 2012)	Number of articles (update from May 1st until January 1st 2012)[b]
Pubmed	(cancer*[tw] OR tumour[tw] OR tumours[tw] OR tumou*[tw] OR carcinom*[tw] OR neoplas*[tw] OR squam*[tw] OR epitheliom*[tw] OR melanom*[tw]) AND (multiple[tw] OR subsequen*[tw] OR second*[tw] OR metachron*[tw]) AND (skin*[tw] OR dermatol*[tw] OR basal[tw] OR baso*[tw] OR cutan*[tw] OR cutis*[tw] OR rodent ulcer*[tw] OR melanom*[tw]) AND (risk[mesh] OR risk*[tw] OR incidence*[tw] OR prevalence*[tw] OR epidemiol*[tw]) AND eng[la] NOT (animals[mesh] NOT humans[mesh])	7,076	409
EMbase	(((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) NEAR/3 (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)):ti,ab,de OR 'second cancer'/syn) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) NEAR/3 (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)):ti,ab,de OR 'skin tumour'/syn OR (rodent NEAR/1 ulcer*):ti,ab,de OR melanom*:ti,ab,de) AND (risk* OR incidence* OR prevalence* OR epidemiol*):ti,ab,de AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)	3,155	304
Web of Science	((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) SAME (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) SAME (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)) OR rodent-ulcer* OR melanom*) AND (risk* OR incidence* OR prevalence* OR epidemiol*)	2,299	
Web of Science[a]	((cancer* OR tumo* OR carcinom* OR neoplas* OR melanom*) NEAR/1 (multiple OR subsequen* OR another OR further OR more OR second* OR metachron*)) AND (((cancer* OR tumo* OR carcinom* OR neoplas* OR squam* OR epitheliom*) NEAR/3 (skin* OR derma* OR basal OR baso* OR cutan* OR cutis*)) OR (rodent NEAR/1 ulcer*) OR melanom*) AND (risk* OR incidence* OR prevalence* OR epidemiol*)		200
Total		**12,530**	**913**
Deduplication		-3,151	-148
Total (after deduplication)		**9,379**	**765**

A comprehensive literature search strategy was performed assisted by a medical librarian of the Erasmus MC University Medical Center, Rotterdam, the Netherlands. On May 5th 2011, Pubmed, Embase, Web of Science and the Cochrane library were searched with database-specific search strings (Supplemental Table 2). On January 18th 2012, an update of the search query (May 1st 2011 until January 1st 2012) was performed. In Figure 1, the selection process of included articles is shown. No relevant articles were found within the Cochrane database. To have insight in grey literature internet search engines were also searched and one additional article was included.[21] Two other articles were handpicked; one after manually checking cross-references[17] and another recent study conducted within our department.[44]

Supplemental Table 2. Search strategy and strings (continued)

Two authors (S.F., MD, PhD and R.L., MD) reviewed independently all titles and/or abstracts (n= 10,147, including 3 handpicked). When an article fulfilled the inclusion criteria, data extraction and quality assessment were independently performed by S.F. and R.L. Disagreements were discussed and solved together in consensus with authors E.V. and T.N..

Legend:

[a] Identical search strings were used for the update within Pubmed and Embase databases. The search string for Web of Science was adjusted due to changes of this database and time was restricted to 2011 and 2012.

[b] Literature search was updated until January 1st 2012, but was performed on January 18th 2012.

Supplemental Table 3A. Adapted Newcastle – Ottawa quality assessment scale for cohort studies

	NOS[a]		Adapted NOS[b]	
Selection				
1	**Representativeness of the exposed cohort**		**Representativeness of the cohort**	
a)	truly representative of the average … (describe) in the community	*	population-based study	**
b)	somewhat representative of the average … in the community	*	population-based study with restrictions (e.g. age limits)	*
c)	selected group of users eg nurses, volunteers	-	hospital-based study	-
d)	no description of the derivation of the cohort	-	no description of the derivation of the cohort	-
2	**Selection of the non exposed cohort**		*Question removed, not applicable in our research question*	
a)	drawn from the same community as the exposed cohort	*		NA
b)	drawn from a different source	-		
c)	no description of the derivation of the non exposed cohort	-		
3	**Ascertainment of exposure**		**Ascertainment of completeness of the studied cohort**	
a)	secure record (eg surgical records)	*	nationwide pathology lab, Cancer Registry	*
b)	structured interview	*	hospital-based	-
c)	written self report	-	written self report	-
d)	no description	-	no description	-
4	**Demonstration that outcome of interest was not present at start of study**		**Certainty of the first skin cancer**	
a)	yes	*	yes, truly first skin cancer, explicitly mentioned in text	*
b)	no	-	no / unknown	-

Supplemental Table 3A. (continued)

Comparability				
1	**Comparability of cohorts on the basis of the design or analysis**		**Comparability of cohorts on the basis of the design or analysis**	
a)	study controls for … (select the most important factor)	*	risk of developing another skin cancer is stratified for sex	*
b)	study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)	*	study controls for any additional factor (e.g. follow-up, age)	*
Outcome				
1	**Assessment of outcome**		**Ascertainment of another skin cancer**	
a)	independent blind assessment	*	record linkage (e.g. cancer registry, nationwide pathology database)	*
b)	record linkage	*	hospital pathology database	*
c)	self report	-	NA (exclusion criteria)	-
d)	no description	-	no description	-
2	**Was follow-up long enough for outcomes to occur**		**Was follow-up long enough for outcomes to occur**	
a)	yes (select an adequate follow up period for outcome of interest)	*	yes (mean/median follow-up time is at least 3 years)	*
b)	no	-	no or unknown	-
3	**Adequacy of follow up of cohorts**		**Adequacy of follow up of cohorts**	
a)	complete follow up - all subjects accounted for	*	complete follow up - all subjects accounted for	*
b)	subjects lost to follow up unlikely to introduce bias - small number lost - > … % (select an adequate %) follow up, or description provided of those lost)	*	subjects lost to follow up unlikely to introduce bias - small number lost - > 80% (select an adequate %) follow up, or description provided of those lost)	*
c)	follow up rate < … % (select an adequate %) and no description of those lost	-	follow up rate < 80% (select an adequate %) and no description of those lost	-
d)	no statement	-	no statement	-

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

[b] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories (except Selection question 1, two stars can be given to population-based studies). A maximum of two stars can be given for Comparability.

Abbreviations: 'NOS'=Newcastle - Ottawa Scale; 'NA'= not applicable

Supplemental Table 3B. Adapted Newcastle – Ottawa quality assessment scale for case-control studies

	NOS[a]		Adapted NOS[b]	
Selection				
1	**Is the case definition adequate**		**Is the case definition (skin cancer patients who developed another skin cancer) adequate**	
a)	yes, with independent validation	*	secure record (e.g. cancer registry, nationwide pathology database)	*
b)	yes, e.g. record linkage or based on self reports	-	hospital-based database	-
c)	no description	-	no description	-
2	**Representativeness of the cases**		**Representativeness of the cases (skin cancer patients who developed another skin cancer)**	
a)	consecutive or obviously representative series of cases	*	population-based study	*
b)	potential for selection biases or not stated	-	population-based study with restrictions (e.g. age limits)	*
c)			hospital-based study	-
d)			no description of the derivation of the cohort	-
3	**Selection of Controls**		**Selection of Controls (skin cancer patients who did not develop another skin cancer)**	
a)	community controls	*	population-based study	*
b)	hospital controls	*	population-based study with restrictions (e.g. age limits)	*
c)	no description	-	hospital-based study	-
d)			no description of the derivation of the cohort	-
4	**Definition of Controls**		**Definition of Controls (skin cancer patients who did not develop another skin cancer)**	
a)	no history of disease (endpoint)	*	no development of another skin cancer	*
b)	no description of source	-	not described / unknown	-
Comparability				
1	**Comparability of cases and controls on the basis of the design or analysis**		**Comparability of cases and controls on the basis of the design or analysis**	
a)	study controls for … (Select the most important factor.)	*	study controls for age	*
b)	study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)	*	study controls for any additional factor (e.g. sex)	*

Supplemental Table 3B. (continued)

Exposure				
1	**Assessment of outcome**		**Ascertainment of another skin cancer**	
a)	secure record (e.g. surgical records)	*	secure record (e.g. cancer registry, nationwide pathology database)	**
b)	structured interview where blind to case/ control status	*	hospital pathology database	*
c)	interview not blinded to case/control status	-	NA	-
d)	written self report or medical record only	-	NA	-
e)	no description	-	no description	-
2	**Same method of ascertainment for cases and controls**		*Question removed, not applicable in our research question*	
a)	yes	*		NA
b)	no	-		
3	**Non-Response rate**		**Non-Response rate**	
a)	same rate for both groups	*	same rate for both groups	*
b)	non respondents described	-	non respondents described	-
c)	rate different and no designation	-	rate different and no designation	-

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

[b] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories (except Exposure question 1, two stars can be given to a secure record). A maximum of two stars can be given for Comparability.

Abbreviations: 'NOS'=Newcastle - Ottawa Scale; 'NA'= not applicable

Supplemental Table 4. Mean cumulative risks (CR)[4,12,16,18,21,23,25,26,37,44,49]

	Number of studies	Mean 1-year cumulative risk (range)	Number of studies	Mean 5-year cumulative risk (range)	Number of studies	Mean 10-year cumulative risk (range)	Number of studies	Mean 15-year cumulative risk (range)	Number of studies	Mean 20-year cumulative risk (range)
Melanoma after melanoma	3	2.4% (0.7-5.5)	8	3.5% (0.6-11.4)	8	5.3% (1.5-10.5)	2	4.6% (4.0-5.2)	3	5.4% (5.0-6.2)
BCC after melanoma	1	1.2% (NA)	2	3.1% (2.6-3.5)	1	5.5% (NA)	1	12.0% (NA)	1	14.0% (NA)
SCC after melanoma	1	0.3% (NA)	2	0.7% (0.4-1.0)	1	2.3% (NA)	1	4.0% (NA)	1	4.0% (NA)

Abbreviations: BCC, basal cell carcinoma; NA, not applicable; SCC, squamous cell carcinoma.

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Part I

Multiple

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CHAPTER 3

Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis

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Eur J Cancer. 2013 Jul;49(10):2365-75.

ABSTRACT

In this systematic review and meta-analysis the risk of a subsequent basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma in patients with a previous keratinocyte carcinoma (KC) was investigated. PubMed, Embase, Web of Science and the Cochrane library were searched for studies published before 1st January 2012 that reported risks (i.e. proportions, cumulative risks or standardised incidence ratios [SIR]) of developing a subsequent BCC, SCC or melanoma in patients with prior KC. 45 articles fulfilled the inclusion criteria. In BCC patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively 29.2% (95% confidence interval (CI) 24.6–34.3%), 4.3% (1.7–10.1%) and 0.5% (0.4–0.8%). The pooled proportion of a subsequent SCC, BCC or melanoma in SCC patients was respectively 13.3% (95% CI 7.4–22.8%), 15.9% (5.6–37.6%) and 0.5% (0.3–0.6%). The pooled SIRs for a subsequent BCC, SCC or melanoma were respectively 17.4 (95% CI 0.0–37.4), 3.2 (0.0–6.5) and 2.4 (2.3–2.6) in BCC and 4.2 (95% CI 2.0–6.5), 15.0 (14.0–16.0) and 2.7 (2.3–3.2) in SCC patients. In the subgroup analyses, strongest differences in risks were found in the continent strata (risks Australia > North America > Europe).

Funding

The Netherlands Organisation for Health Research and Development (ZonMw), Project Numbers 152001013/VIDI 91711315.

INTRODUCTION

Keratinocyte carcinoma (KC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, is the most common cancer in Caucasian populations with increasing incidence rates across North America, Australia and Europe.[1]

Patients with prior KC are at increased risk of developing subsequent cutaneous (pre)-malignancies (Supplemental Table 1). The number of population-based studies investigating risks of subsequent KC is low, because KC is often not or partially included in national or regional cancer registries. Marcil and Stern, 2000 estimated the risk of a subsequent BCC and SCC in patients with a history of KC in a meta-analysis including 17 studies.[2] A 3-year cumulative risk of 44% for BCC after BCC and 18% for SCC after SCC was observed. However, these analyses were not based on a systematic review, studies were not critically appraised and melanoma was excluded. After 2000, multiple new studies on the risk of subsequent cutaneous malignancies among patients with prior cutaneous malignancies have been published.

In this systematic review and meta-analysis the risk of developing a subsequent BCC, SCC or melanoma in patients with previous KC was investigated to give a complete view on the currently available data regarding this topic. It may serve as a guide for patients and clinicians and form a basis for (future) skin cancer care and guidelines, health care policy makers and public health campaigns.

METHODS

This study was conducted to examine risk estimates of developing a subsequent BCC, SCC or melanoma in patients with a history of BCC, SCC or melanoma. This systematic review and meta-analysis is limited to the risk of developing a subsequent BCC, SCC or melanoma in patients with previous KC. In this study, the risks of these cutaneous malignancies amongst melanoma patients were excluded due to the large amount of eligible papers. Risks of a subsequent BCC, SCC or melanoma after a melanoma will be described in a separate study. Results were reported according to the PRISMA statement for reporting systematic reviews and meta-analyses of epidemiological studies.[3]

Search strategy

See Supplemental Table 2.

Inclusion and exclusion criteria

Studies were included when meeting the following inclusion criteria: (1) patients with a previous BCC or SCC were followed over time for the development of a subsequent BCC,

SCC or melanoma and an associated proportion, standardised incidence ratio (SIR) or cumulative risk (CR) was provided; (2) skin cancer diagnoses were histopathologically confirmed in more than 80% of the cases; (3) reported in English.

Of the above mentioned eligible risk estimates, proportion was the most frequently reported in the literature, however, in contrast with CR and SIR, this estimate is little informative as it is not time-specific, does not account for the competing risk 'death' and does not compare to the risk in the non-KC population.

Studies were excluded when meeting the following exclusion criteria: (1) specific patient populations who were at extreme risk of developing cutaneous malignancies (e.g. transplant patients or genodermatoses); (2) more than 10% of the first or subsequent cutaneous malignancies were recurrences or no adequate case definition was made (e.g. no distinction between recurrences and first or subsequent cutaneous malignancies); (3) animal studies; (4) review, editorial, meta-analysis, consensus, guideline, case-reports or case-series; (5) only reporting cutaneous malignancies on specific anatomical sites.

Study selection

The following seven tumour combinations of interest were extracted: BCC after BCC, SCC after BCC, melanoma after BCC, BCC after SCC, SCC after SCC, melanoma after SCC and KC after KC.

The majority of the included articles reported separate observations for multiple tumour combinations.

If identical populations were described in several publications within the same or overlapping time period, these publications were compared and the study with the most extensive results was included. An exception was made for two studies with an overlapping study population, which provided different risk measurements.[4,5]

Data extraction

See Supplemental Table 1.

Quality assessment

The study quality was assessed by using adapted criteria (Supplemental Table 3) from the Newcastle–Ottawa quality assessment scale (NOS) which is a quality assessment tool for cohort and case–control studies in systematic reviews and meta-analyses.[6] The NOS is divided within three grouping items: selection (four points), comparability (two points) and outcome (three points). The maximum score of an article was 9 points. The risk of bias was considered moderate or low when the overall sum was five points or higher.[7]

Statistical methods

The primary outcome of interest of this meta-analysis was the proportion of BCC, SCC or KC patients that developed a subsequent cutaneous malignancy (i.e. BCC, SCC, melanoma or KC separately). This proportion was calculated by dividing the number of patients with a subsequent skin cancer by the total number of followed patients. The second outcome of interest was SIR, calculated as the observed number of patients that developed a subsequent cutaneous malignancy by the expected number of patients in the general population (i.e. background incidence). CR was calculated by dividing the number of patients that developed a subsequent cutaneous maliganancy by the total number of patients alive after a certain time period.

Pooled estimates for proportion and SIR with 95% confidence intervals (95% CI) were calculated with a random effects model as proposed by DerSimonian and Laird because of high study heterogeneity (I^2 index > 75%).[8,9] In this model, the inverse of standard errors of proportion and SIR from the individual studies combined with the between study variation were used as weights. Only a limited number of studies provided a CR and most of them provided a 5-year CR. In addition, confidence intervals and life tables were often lacking. Therefore, it was not possible to calculate a pooled CR. However, to give an overview of the available CR data, the available 5-year CR was averaged.

Subgroup analyses (only performed when number of separate observations per tumour combination ≥5) and sensitivity analyses were performed to understand the 'robustness' of the data and to find possible sources for study heterogeneity.[10] In the subgroup analyses the following study characteristics were compared, overall NOS score <5 versus ≥5, population- versus hospital-based, in- versus exclusion of in situ cutaneous malignancies, studies that explicitly stated to follow patients with a 'first' BCC, SCC or KC versus studies without this statement (i.e. unknown if the patients under study were 'new' skin cancer patients or not). Stratification by study continent (i.e. Australia, North America and Europe) was also performed. Publication bias was statistically assessed by funnel plots and the Eggers' test (Supplemental Figure 1).[11] All statistical analyses were performed using the software package Comprehensive meta-analysis (version 2.2) and SPSS statistical software (version 18 for Windows, SPCC Inc, Chicago, Illinois).

RESULTS

The literature search identified 10,147 articles of which 233 were found potentially eligible based on title or abstract. Of the 233 fully read articles, 45 were eligible in the prior KC analysis (Figure 1). In these 45 articles (Supplemental Table 1), a total of 74 separate observations (i.e. in most cases one article contained information on multiple tumour

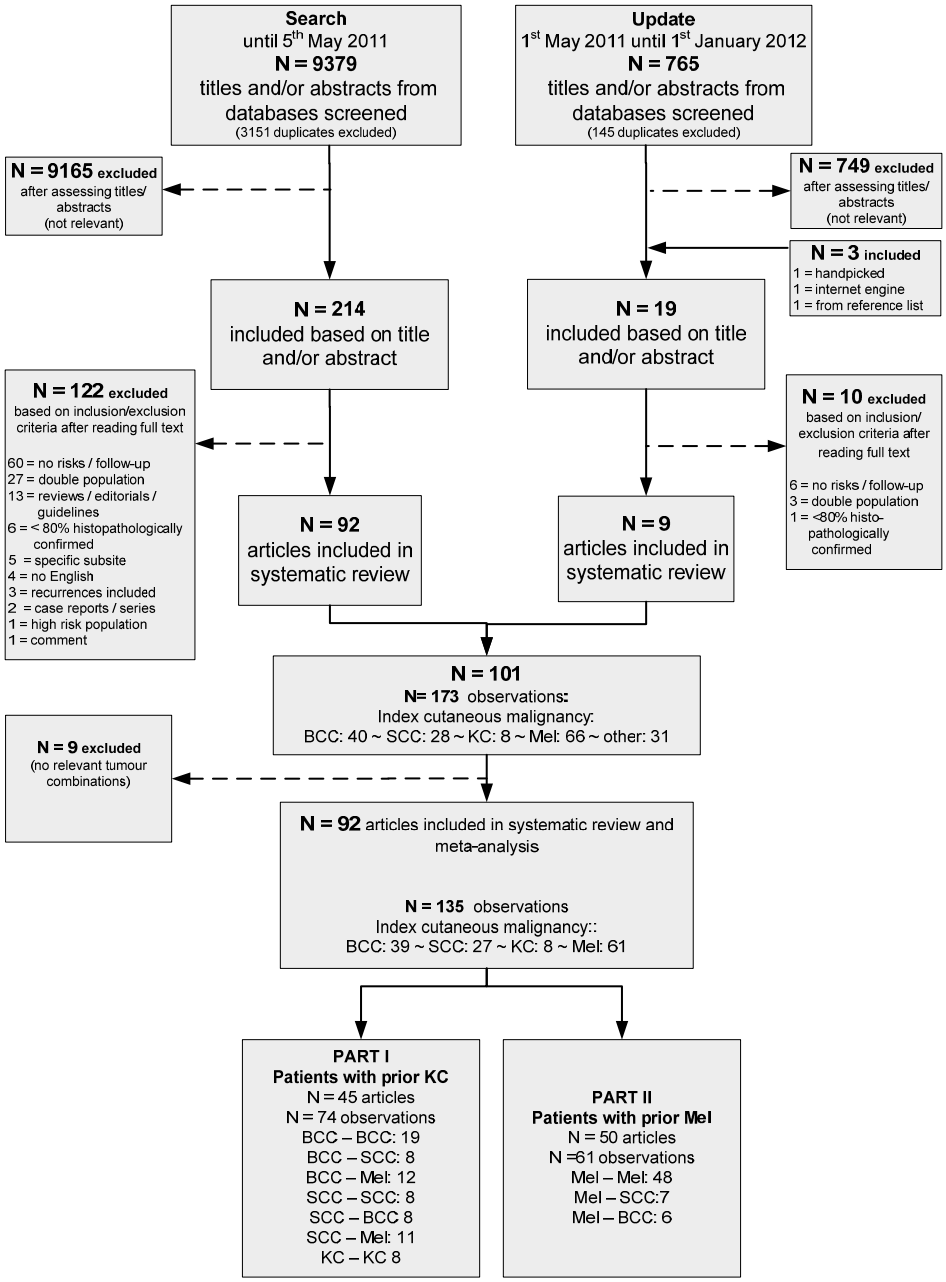


Figure 1. Selection process of included articles

combinations) were reported for the seven possible tumour combinations. Of these 74 separate observations, 39 had BCC as index tumour, 27 SCC and eight KC.

The 45 articles in this meta-analysis included 43 cohort and two case–control studies. More than half of the articles were population-based (n = 24), of which 15 included cancer registry data. In total, 11 articles had a prospective, while 34 had a retrospective study design. For 41 articles the full text was available, whereas for four only abstracts[12-15] were retrieved. Fourteen countries were represented in the articles, corresponding to three continents (i.e. Australia, North America and Europe). Of the full articles, 44% was appraised with a high quality score (≥5 NOS score); 47% of the 74 separate observations also received this score.

BCC as index tumour

29 articles (Supplemental Table 1A), corresponding to 39 separate observations, included patients with a BCC as the index tumour. In these patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively 29.2% (95% CI 24.6–34.3%; n = 19), 4.3% (1.7–10.1%; n = 7) and 0.5% (0.4–0.8%; n = 11) (Figure 2A–C). Pooled estimates within the subgroup analyses (i.e. study quality, study design, in situ cutaneous malignancies in- or excluded, 'first' cutaneous malignancy yes/no, continents) showed similar results with overlapping confidence intervals (Table 1).

In the forest plots, the Australian study by Richmond-Sinclair[16] was an outlier, with almost 58% of the BCC patients developing another BCC, compared to the other 18 studies (Figure 2A). Two studies conducted in North America[17,18] presented relatively high proportions of patients developing a subsequent SCC (after BCC) compared to the other European studies (Figure 2B). Also, melanoma risk after BCC was higher in United States (US) studies,[18,19] compared to the European and one Canadian study[20] (Figure 2C).

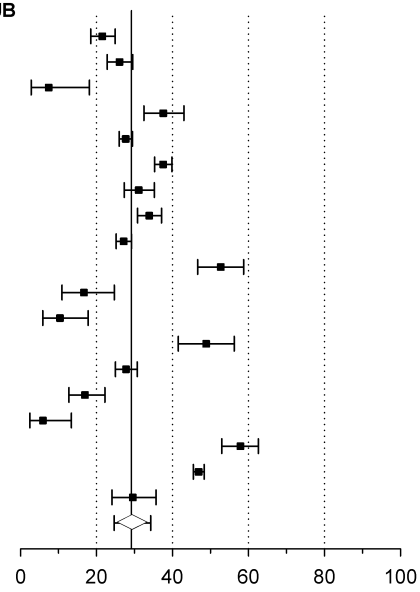
The previous observations were confirmed within the subgroup analyses by continent (Table 1). For BCC after BCC, the highest pooled proportion for BCC after BCC was found in Australia (n = 1, 57.9%), followed by North America (n = 6, 32.5%) and Europe (n = 12, 27.3%). For SCC and melanoma after BCC the highest pooled proportion was observed in North America followed by Europe (Table 1). In the latter two tumour combinations, no data from Australia were available.

In addition, two studies explicitly stated to have age restrictions, Cox[21] and Kiiski et al.[22] and two studies only contained data on low risk BCC (Mc Loone et al.[23] and Pulido et al.[14]). After excluding these four articles in a sensitivity analysis, the pooled proportion increased to 32.5% (95% CI 27.2–38.3).

Pooled SIRs, which compares the observed incidence to the expected incidence in the general population, showed that patients with a BCC had a seventeen fold (SIR 17.4

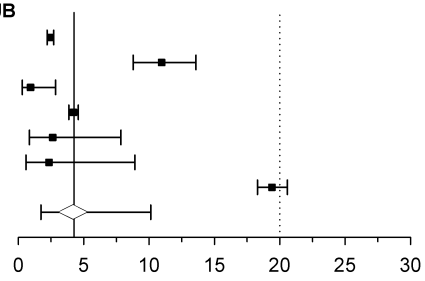
A

Study	Year	Proportion (%)	95% LB	95% UB
Biro	1975	21.50	18.46	24.88
Chuang	1990	26.03	22.81	29.52
Cox	1992	7.41	2.81	18.13
Di Landro	2004	37.58	32.45	43.00
Flohil	2011	27.67	25.94	29.46
Karagas	1992	37.52	35.27	39.83
Kiiski	2010	31.11	27.29	35.20
Lear	1997	33.88	30.78	37.12
Levi	2006	27.14	25.17	29.20
Marghoob	1993	52.69	46.61	58.69
McLoone	2006	16.67	10.89	24.66
Pulido	2010	10.38	5.84	17.77
Ramachandran	2001	27.75	24.96	30.73
Ramachandran	2009	48.85	41.50	56.25
Reizner	1993	16.94	12.72	22.20
Revenga	2004	5.88	2.47	13.36
Richmond-Sinclair	2010	57.86	52.96	62.60
Schreiber	1990	46.90	45.47	48.33
van Iersel	2005	29.54	24.08	35.65
Pooled proportion		**29.21**	**24.63**	**34.25**



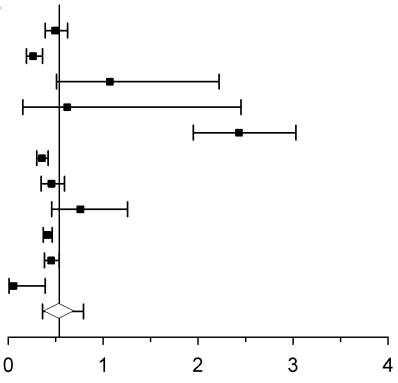
B

Study	Year	Proportion (%)	95% LB	95% UB
Cantwell	2009	2.44	2.20	2.71
Chuang	1990	10.96	8.79	13.59
DiLandro	2004	0.93	0.30	2.85
Levi	1998	4.22	3.87	4.59
McLoone	2006	2.63	0.85	7.84
Revenga	2004	2.35	0.59	8.92
Schreiber	1990	19.40	18.30	20.58
Pooled proportion		**4.26**	**1.73**	**10.12**



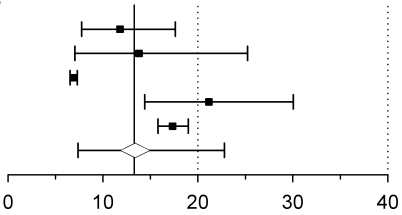
C

Study	Year	Proportion (%)	95% LB	95% UB
Bower	2000	0.49	0.39	0.63
Cantwell	2009	0.26	0.19	0.36
Chuang	1990	1.07	0.51	2.22
DiLandro	2004	0.62	0.16	2.45
Friedman	2000	2.43	1.95	3.03
Frisch	1996	0.36	0.30	0.42
Levi	1998	0.46	0.35	0.59
Lindelof	1991	0.76	0.46	1.26
Milan	2000	0.41	0.37	0.46
Nugent	2005	0.45	0.38	0.54
Troyanova	2002	0.05	0.01	0.39
Pooled proportion		**0.54**	**0.36**	**0.79**



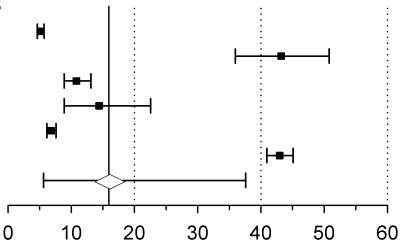
D

Study	Year	Proportion (%)	95% LB	95% UB
Chuang	1990	11.80	7.76	17.63
Chuang	1995	13.79	7.05	25.23
Dong	2001	6.90	6.54	7.29
Kemmett	2004	21.15	14.40	30.05
Schreiber	1990	17.34	15.80	18.98
Pooled proportion		**13.30**	**7.39**	**22.78**



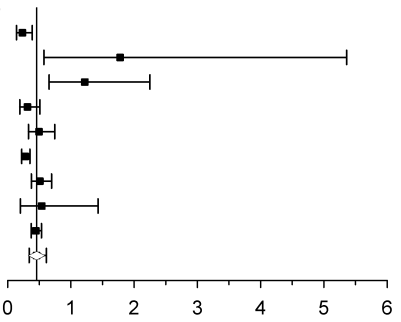
E

Study	Year	Proportion (%)	95% LB	95% UB
Cantwell	2009	5.16	4.64	5.72
Chuang	1990	43.20	35.93	50.76
Efird	2002	10.83	8.88	13.14
Kemmett	2004	14.42	8.89	22.56
Levi	1997	6.83	6.14	7.60
Schreiber	1990	42.97	40.92	45.06
Pooled proportion		**15.94**	**5.64**	**37.57**



F

Study	Year	Proportion (%)	95% LB	95% UB
Cantwell	2009	0.23	0.14	0.39
Chuang	1990	1.78	0.57	5.36
Efird	2002	1.22	0.66	2.25
Frisch	1995	0.31	0.19	0.51
Levi	1997	0.50	0.33	0.75
Maitra	2005	0.28	0.22	0.35
Nugent	2005	0.51	0.38	0.70
Troyanova	2002	0.54	0.20	1.43
Wassberg	1999	0.45	0.37	0.54
Pooled proportion		**0.46**	**0.34**	**0.61**



G

Study	Year	Proportion (%)	95% LB	95% UB
Czarnecki	2002	67.80	63.50	71.80
Graells	2004	22.40	19.10	26.20
Raasch	2002	38.50	37.30	39.70
Schinstine	2001	39.30	34.90	44.00
Schreiber	1990	50.00	48.80	51.20
Veien	2001	20.30	17.10	24.00
Veien	2001	27.10	23.80	30.70
Pooled proportion		**37.00**	**29.00**	**45.80**

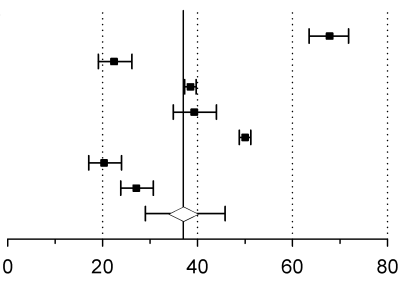


Figure 2. Risk (%) of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma[4, 5, 12-29, 49, 51-53, 56-72]

A Basal cell carcinoma (BCC) after BCC

B Squamous cell carcinoma (SCC) after BCC

C Melanoma after BCC

D SCC after SCC

E BCC after SCC

F Melanoma after SCC

G Keratinocyte carcinoma (KC) after KC

[0.0–37.4; *n* = 2] increased risk of a subsequent BCC compared to the general population. This was followed by SCC (3.2 [0.0–6.5]; *n* = 3) and melanoma (2.4 [2.3–2.6]; *n* = 5) after BCC (Table 2).

The mean 5-year cumulative risk (CR) for BCC after BCC was 36.2% (*n* = 7, range 11.0–49.9%). No 5-year CR was available for the other tumour combinations with BCC as the index tumour (Table 3).

SCC as index tumour

17 articles (Supplemental Table 1B), corresponding to 27 separate observations, described patients with SCC as the index tumour. The pooled proportion of a subsequent SCC, BCC or melanoma in SCC patients was respectively, 13.3% (95% CI 7.4–22.8; *n* = 5), 15.9% (5.6–37.6; *n* = 6) and 0.5% (0.3–0.6; *n* = 9) (Figure 2D–F). In the five subgroup analyses, similar results with overlapping CI compared to the overall pooled proportions were observed (Table 1). The continent with the highest pooled proportion for SCC, BCC and melanoma after SCC was North America [15.3% (11.7–19.7; *n* = 3), 29.1% (11.0–57.7; *n* = 3) and 1.3% (0.8–2.2; *n* = 2), respectively]. No data were available for Australia.

The studies performed in the USA, Schreiber et al.[17] and Chuang et al.[24], except the study by Efird et al.[25] had with 43% the highest proportions for BCC after SCC and seemed outliers compared to the other four studies in this tumour combination. After excluding these two studies in a sensitivity analysis, the pooled proportion for BCC after SCC decreased to 8.0% (5.8–11.4). In melanoma after SCC, the highest proportions were found by relatively small studies such as Chuang et al.[24] (*n* = 189) and Efird et al.[25] (*n* = 822), whereas others had study sizes of more than 1,000 patients, except Troyanova et al.[12] (*n* = 741) (Supplemental Table 3B). After excluding Chuang et al.[24] and Efird et al.[25] in the sensitivity analysis, the pooled proportion for melanoma after SCC decreased to 0.4% (0.3–0.5).

A high SIR of 15.0 (14.0–16.0) was observed for SCC after SCC, however based on just one study (Table 2). The SIRs for BCC and melanoma after SCC were also increased, respectively 4.2 ([95% CI 2.0–6.5]; *n* = 3) and 2.7 ([95% CI 2.3–3.2]; *n* = 5).

The mean 5-year CR for SCC after SCC was 37.0% (*n* = 3, range 30.0–50.0%) and comparable to the mean 5-year CR of BCC after SCC (39.3% [*n* = 2, range 6.0–72.5%]). No 5-year CR was available for tumour combination melanoma after SCC (Table 3).

KC as index tumour

Seven articles (Supplemental Table 1C), including eight separate observations, investigated KC (BCC and SCC combined) after KC. This resulted in a pooled proportion of 37.0% (95% CI 29.0–45.8; *n* = 7). Czarnecki et al.[26] from Australia, the study with the longest mean follow-up time (i.e. 10 years), had with 67.8% a high proportion of KC patients developing another KC compared to another Australian study with 38.5% (Raasch and Buettner[27]) and studies from North America and Europe (Figure 2G).

Table 1. Overview of pooled estimates of proportion with subgroup analyses for all observations

	BCC after BCC (%, 95%CI)	SCC after BCC (%, 95%CI)	Mel after BCC (%, 95%CI)	BCC after SCC (%, 95%CI)	SCC after SCC (%, 95%CI)	Mel after SCC (%, 95%CI)	KC after KC (%, 95%CI)
N studies	**19**	**7**	**11**	**6**	**5**	**9**	**7**
Pooled estimate proportion	**29.2 (24.6-34.3)**	**4.3 (1.7- 10.1)**	**0.5 (0.4-0.8)**	**15.9 (5.6-37.6)**	**13.3 (7.4-22.8)**	**0.5 (0.3-0.6)**	**37.0 (29.0-45.8)**
NOS ≥5 N	6	4	9	4	3	8	1
Pooled proportion	31.1 (23.0-40.6)	7.0 (2.3-19.6)	0.5 (0.3-0.8)	17.9 (4.6-49.5)	11.3 (5.3-22.5)	0.4 (0.3-0.5)	50.0 (48.8-51.2)
NOS <5 N	13	3	2	2	2	1	6
Pooled proportion	27.8 (21.9-34.6)	1.7 (0.9-3.4)	0.7 (0.5-1.2)	11.5 (9.0-14.3)	18,4 (12.3-26.7)	1.2 (0.6-2.3)	34.9 (25.0-46.3)
Population-based N studies	8	4	9	4	4	8	2
Pooled proportion	29.7 (22.0-38.7)	7.0 (2.3-19.6)	0.5 (0.3-0.8)	17.9 (4.6-49.5)	11.8 (6.1-21.6)	0.4 (0.3-0.5)	44.2 (33.3-55.6)
Hospital based N studies	11	3	2	2	1	1	5
Pooled proportion	29.0 (23.6-35.0)	1.7 (0.9-3.4)	0.7 (0.5-1.2)	11.5 (9.1-14.3)	21.2 (14.3-30.1)	1.2 (0.7-2.3)	34.2 (19.7-52.3)
Excluding in situ N studies	15	4	6	5	5	4	7
Pooled proportion	29.7 (24.1-35.9)	5.1 (1.5-15.6)	0.6 (0.3-1.1)	17.2 (5.1-44.0)	13.0 (7.4-22.8)	0.4 (0.2-0.7)	37.0 (29.0-45.8)
Including in situ N studies	0	1	0	1	0	1	0
Pooled proportion	NA	0.9 (0.3-2.9)	NA	10.8 (8.9-13.1)	NA	1.2 (0.7-2.3)	NA
In situ, unknown included N studies	4	2	5	0	0	4	0
Pooled proportion	27.8 (20.1-37.1)	6.0 (1.3-23.4)	0.5 (0.3-0.6)	NA	NA	0.5 (0.4-0.5)	NA

Table 1 (continued)

	BCC after BCC (%, 95%CI)	SCC after BCC (%, 95%CI)	Mel after BCC (%, 95%CI)	BCC after SCC (%, 95%CI)	SCC after SCC (%, 95%CI)	Mel after SCC (%, 95%CI)	KC after KC (%, 95%CI)
First tumor yes **N studies**	9	4	7	4	3	9	1
Pooled proportion	25.8 (22.7-29.2)	4.5 (2.5-7.9)	0.4 (0.3-0.5)	12.0 (6.0-22.5)	9.7 (6.0-15.5)	0.5 (0.3-0.6)	39.3 (34.9-44.0)
First tumor no **N studies**	7	3	2	1	1	0	6
Pooled proportion	42.9 (36.7-49.4)	3.9 (0.5-27.9)	1.5 (0.4-5.2)	43.0 (40.9-45.1)	17.3 (15.8-19.0)	NA	36.7 (27.9-46.4)
First tumor unknown **N studies**	3	0	2	1	1	0	0
Pooled proportion	20.6 (14.5-28.4)	NA	0.5 (0.3-1.0)	14.4 (8.9-22.6)	21.2 (14.4-30.1)	NA	NA
Europe **N studies**	12	5	9	3	2	7	3
Pooled proportion	27.3 (23.8-31.2)	2.7 (1.7 – 4.2)	0.4 (0.3-0.5)	7.2 (5.2-9.8)	12.1 (3.8-32.7)	0.4 (0.3-0.5)	23.3 (19.5-27.5)
USA **N studies**	6	2	2	3	3	2	2
Pooled proportion	32.5 (24.0-42.2)	14.8 (8.3-25.2)	1.7 (0.8-3.8)	29.1 (11.0-57.7)	15.3 (11.7-19.7)	1.3 (0.8-2.3)	44.8 (34.7-55.4)
Australia **N studies**	1	0	0	0	0	0	2
Pooled proportion	57.9 (53.0-62.6)	NA	NA	NA	NA	NA	53.3 (25.9-78.9)

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; Mel, melanoma; N, number; NA, not applicable; NOS, Newcastle – Ottawa scale; SCC, squamous cell carcinoma; USA, United States of America.

Table 2. Overview of pooled estimates of standardised incidence ratios (SIR)

	BCC after BCC (95%CI)	SCC after BCC (95%CI)	Mel after BCC (95%CI)	BCC after SCC (95%CI)	SCC after SCC (95%CI)	Mel after SCC (95%CI)	KC after KC (95%CI)
N studies	**2**	**3**	**6**	**3**	**1**	**5**	**0**
Pooled estimate SIR	**17.4 (0.0-37.4)**	**3.2 (0.0-6.5)**	**2.4 (2.3-2.6)**	**4.2 (2.0-6.5)**	**15.0 (14.0-16.0)**	**2.8 (2.3-3.2)**	**NA**

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; KC, keratinocyte carcinoma; Mel, melanoma; NA, not applicable; N, number; SCC, squamous cell carcinoma; SIR, standardised incidence ratio.

Table 3. Mean 5 – year cumulative risks (CR)

	Number of studies	Mean 5-year cumulative risk (range)
BCC after BCC	7;[5,15,28,49-52]	36.2% (11.0 – 49.9)
SCC after BCC	0	NA
Mel after BCC	0	NA
BCC after SCC	2;[53-54]	39.3% (6.0 – 72.5)
SCC after SCC	3;[28,54-55]	37.0% (30.0 – 50.0)
Mel after SCC	0	NA
KC after KC	2;[28,29]	36.2% (22.4 – 50.0)

Abbreviations: BCC, basal cell carcinoma; CR, cumulative risk; Mel, melanoma; NA, not applicable; SCC, squamous cell carcinoma

Although based on one study, subgroup analysis by continent (Table 1) showed that the highest pooled proportion was found in Australia with 53.3% (n = 2), followed by North America (44.8%; n = 2) and Europe (23.3%; n = 3). No studies reported SIR as risk measurement for KC after KC.

The mean 5-year CR for KC after KC was 36.2% (n = 2, range 22.4–50.0%).[28,29]

DISCUSSION

This systematic review and meta-analysis emphasises that a KC history is among the strongest risk factors for developing another BCC, SCC or melanoma. The highest risk estimates were found for subsequent cutaneous malignancies of the same type, especially for BCC in which 29% of patients had subsequent BCCs. The increased risk of developing subsequent BCC, SCC and melanoma after a first KC suggests a partially common aetiology of UV-induced field cancerisation and genetic predisposition among these three types of skin cancer.[30,31] In contrast, the observation that people were most likely to develop an identical type of malignancy suggests that there are differences in carcinogenesis and associated risk factors among the three most common skin cancers.

A KC history seems to be among the highest risk factors for developing a subsequent KC, and almost comparable to the risk of transplant recipients, radiotherapy treated patients and those exposed to high doses of psoralen combined with ultraviolet A (PUVA).[32-36] Compared to these specific patient populations with an iatrogenic risk of developing skin cancer, the number of patients with a history of KC is enormous and constantly increasing implying a huge impact on health care services. Since primary prevention appears to be unsuccessful in reducing the incidence of skin cancer, secondary prevention strategies in which patients with a KC are informed about future risk, motivated to perform self examinations and have annual total body skin examinations for 3–5 years by trained physicians or nurse practitioners in order to detect new lesions early seems appropriate.

Both BCC and SCC patients also had increased SIRs for developing melanoma (2.4 and 2.7 respectively), which is in accordance with a previous systematic review.[37] Unfortunately, in this review, KC was not included as second primary cancers. These increased risks should alert clinicians and KC patients because early detection of a subsequent melanoma may decrease melanoma-associated mortality.

Subgroup analyses

BCC, SCC and melanoma are all strongly associated with UV exposure and the incidence rates of a primary skin cancer depends on geographic latitude.[38,39] After stratifying for continent, effect sizes of developing subsequent skin cancers after a first KC were the highest for Australia, followed by North America and Europe as expected by the decreasing UV-levels among primarily Caucasian populations. Therefore, the pooled risk estimates of all studies combined should be interpreted with caution because it is biased by geographic location limiting the generalisability of the results. To maximise external validity of this meta-analysis, ideally, it would be necessary to include many studies with identical study designs and large study populations for each tumour combination in each continent to provide location-specific estimates.[40] Here, only a limited number of countries (n = 14) and continents (n = 3) were available and the number of studies in some geographic areas was low. Although we performed subgroup analyses by continents, differences in the distribution of people's characteristics such as pigmentation status (i.e. eye-, hair- and skin-colour) were not accounted for further affecting the generalizibility. No pooled estimates could be calculated for Africa, Asia and inhabitants of the Middle-East. However, considering the darker pigmentation status of these inhabitants, primary and multiple cutaneous malignancies might be a smaller public health problem in these regions.

Consequences and follow-up

Recently, the US preventative task force recommended a case-finding approach in the screening of skin cancer.[41] Although total body skin examinations of all patients visiting a physician may not be feasible in clinical practice, it is warranted in patients with a history of KC because of their extremely high risk. Other important reasons for following patients with cutaneous malignancies are for psychosocial support, (early) detection of a local recurrence for BCC and to a lesser extent of SCC and progression of SCC and melanoma to the draining lymph nodes and visceral organs.[42] Frequency and duration of follow-up of KC patients remains controversial, but from the perspective of developing subsequent cutaneous malignancies follow-up seems desirable for at least 3–5 years annually.[43]

Strengths and limitations

This is the largest systematic review and meta-analysis available on risk of subsequent skin cancer after a BCC or SCC. To ensure high quality reporting, the PRISMA guidelines were used.[3] The pooled risk estimates presented for all tumour combinations are probably underestimated, because some BCCs may be diagnosed clinically without histological confirmation.[44] This problem is almost non-existent for melanoma and SCC, because these cutaneous malignancies have a higher metastatic potential than BCC and are usually surgically treated and histologically confirmed. A recent Dutch study observed that during a mean follow-up of 6 years only 7% of the subsequent BCC in patients with a prior histologically confirmed BCC were clinically diagnosed, indicating that the degree of underestimation of our data is relatively limited.[45]

The risk estimate proportion was the most frequently reported estimate in the literature describing risks of subsequent cutaneous malignancies, but has the disadvantage that it is not time-specific nor does it account for the competing risk 'death'. A relative risk that is much more informative about the risk in the study population compared to the general population (SIR) and an unbiased risk over time (CR) that controls for the number of patients that died during follow-up (i.e. competing risks) are preferred in subsequent (cutaneous) malignancy research.[46] Unfortunately, the number of studies providing SIRs of the tumour combinations of interest was low, which may be a KC specific problem. Most cancer registries do not register BCCs and those that do reliably report the first but not the subsequent BCCs because of the required resources and 'coding' difficulties.[43,47] Therefore, the risk of a subsequent BCC or SCC was mostly based on smaller studies that may have inflated the pooled proportions by selection bias. Also, no pooled CR estimates were calculated because only a few studies reporting the risk of BCC and SCC after a first KC provided this risk measurement. In contrast, studies investigating the risks of subsequent melanomas were more often larger cancer registry studies than studies investigating the risk of a subsequent BCC or SCC in patients with prior KC limiting the aforementioned limitations.

Publication bias is likely to be minimal because the risk estimates of developing a subsequent cutaneous malignancy are probably increased in all studies, as illustrated in this review, minimising negative findings and thus publication bias.[40] Furthermore, publication bias was unlikely due to symmetrical funnel plots and non-significant Egger's tests. The systematic literature search was done by a medical librarian using a string and included congress abstracts and monographs (i.e. 'grey literature').[48] However, language bias may have had an effect because only studies reported in English were eligible. To control for multiple publication bias, only the study that presented the most extensive results or had the longest follow-up was included.

CONCLUSION

A history of a prior KC is a very strong predictor for developing a subsequent BCC and SCC and to a lesser extent melanoma. Secondary prevention (early detection of subsequent episodes of the disease) is pivotal in patients with a prior KC. Patients should be well informed about future risk and require adequate follow-up by physicians.

ACKNOWLEDGEMENTS

We would like to thank Louis Volkers (medical librarian) from the Erasmus MC University Medical Center Rotterdam, the Netherlands for assistance in developing an accurate search strategy.

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SUPPLEMENTAL TABLES AND FIGURES

Supplemental Figure 1. Funnel plot with Egger's test of studies reporting a proportion (%)
A Basal cell carcinoma (BCC) after BCC (p-value 0.06)
B Squamous cell carcinoma (SCC) after BCC (p-value 0.6)
C Melanoma after BCC (p-value 0.7)
D SCC after SCC (p-value 0.4)
E BCC after SCC (p-value 0.8)
F Melanoma after SCC (p-value 0.3)
G Keratinocyte carcinoma (KC) after KC (p-value 0.4)

See http://www.sciencedirect.com/science/article/pii/S0959804913002128 .

Supplemental Table 1. Study characteristics[a]

A Basal cell carcinoma (BCC) as index tumor

	Reference number	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% subsequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
BCC after BCC	[56]	1975	USA	1966 - 1971	Retrospective	Cohort	No	H	-	628	21.5	-	-	-	0	0	0	0
(n= 19)	[18]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	26.0	65	5	-	4	0	2	6
	[21]	1992	UK	1979 - 1989	Retrospective	Cohort	Yes	H	15 - 34 year of age	54	7.4	30	1	-	3	0	1	4
	[57]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	37.6	68	6	-	0	1	1	2
	[51]	2011	Netherlands	2004 - 2009	Retrospective	Cohort	No	P	-	2,483	27.7	65	5	12,297	4	2	3	9
	[28]	1992	USA	1980 - 1989	Prospective	Cohort	No	H	Multi - center trial	1,735	37.5	-	5	-	0	2	1	3
	[22]	2010	Netherlands	1990 - 2007	Prospective	Cohort	No	P	> 55 year of age	524	31.1	69	12	6,274	3	2	2	7
	[52]	1997	UK	1991 - 1995	Retrospective	Cohort	No	H	-	856	33.9	68	-	-	1	0	0	1
	[49]	2006	Switzerland	1976 - 2003	Retrospective	Cohort	Yes	P	-	1,868	27.1	69	-	20,261	4	2	2	8
	[15]	1993	USA	-	Retrospective	Cohort	No	H	Whites	260	52.7	59	7	-	0	1	2	3
	[23]	2006	UK	1999 - 2000	Retrospective	Cohort	No	H	Only low risk BCC	114	16.7	67	-	196	0	0	1	1
	[14]	2010	Spain	1997 - 2007	Retrospective	Cohort	No	H	Only solid BCC	106	10.4	66	10	-	0	0	2	2
	[4]	2001	UK	1991 - 1998	Prospective	Cohort	No	H	-	926	27.8	-	-	-	0	0	0	0
	[5]	2009	UK	1991 - 1998	Prospective	Cohort	No	H	-	174	48.9	-	5	-	0	0	2	2
	[58]	1993	USA	1983 - 1987	Prospective	Cohort	No	P	-	242	16.9	57	5	71,888	2	0	1	3
	[59]	2004	Spain	1998 - 2001	Prospective	Cohort	No	H	-	85	5.9		3	-	1	0	2	3
	[16]	2010	Australia	1992 - 2007	Prospective	Cohort	No	P / field trial	-	401	57.9	60	-	-	1	1	1	3
	[17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	4,670	46.9	-	-	-	3	1	1	5
	[50]	2005	Netherlands	1993 - 1998	Retrospective	Cohort	No	H	-	237	29.5	-	3.1	-	1	2	2	5

Supplemental Table 1. (continued)

	Reference number	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% subsequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
SCC after BCC	[60]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	14,442	2.4	68	4	-	4	1	3	8
(n= 8)	[18]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	11.0	65	-	-	4	0	1	5
	[57]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	0.9	68	6	-	0	1	1	2
	[61]	1998	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	11,878	4.2	68	-	76,510	4	2	2	8
	[23]	2006	UK	1999 - 2000	Retrospective	Cohort	No	H	Only low risk BCC	114	2.6	67	-	196	0	0	1	1
	[76]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	[59]	2004	Spain	1998 - 2001	Prospective	Cohort	No	H	-	85	2.4	-	3	-	1	0	2	3
	[17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	4,670	19.4	-	-	-	3	1	1	5
Melanoma	[62]	2000	UK	1981 - 1995	Retrospective	Cohort	Yes	P	-	13,961	0.5	-	-	117,939	4	1	2	7
after BCC	[60]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	14,442	0.3	68	4	-	4	1	3	8
(n= 12)	[18]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	657	1.1	65	-	-	4	0	1	5
	[57]	2004	Italy	1994 - 2002	Retrospective	Cohort	No	H	-	322	0.6	68	6	-	0	1	1	2
	[19]	2000	USA	1974 - 1997	Retrospective	Case - control	No	P	-	3,164	2.4	-	11	-	2	2	2	6
	[63]	1996	Denmark	1978 - 1991	Retrospective	Cohort	Yes	P	-	37,674	0.4	68	4	190,945	4	2	3	9
	[61]	1998	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	11,878	0.5	68		76,510	4	2	2	8
	[64]	1991	Sweden	1971 - 1983	Retrospective	Cohort	Partly	H	-	1,973	0.8	68	7	12,867	1	1	2	4
	[65]	2000	Finland	1953 - 1995	Retrospective	Cohort	Yes	P	-	71,924	0.4	-	-	625,144	4	2	2	8
	[20]	2005	Canada	1956 - 2000	Retrospective	Cohort	Yes	P	-	28,956	0.5	67	-	282,814	4	2	1	7
	[76]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	[12]	2002	Bulgaria	1993 - 2000	Retrospective	Cohort	Yes	P	-	1,820	0.1	-	-	15,856	4	1	2	7

Supplemental Table 1. (continued)

B Squamous cell carcinoma (SCC) as index tumor

	Reference number	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% subsequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
SCC after SCC	[24]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	169	11.8	71	4	-	4	0	1	5
(n=8)	[66]	1995	USA	1983 - 1987	Prospective	Cohort	No	P	-	58	13.8	66	5	71,888	2	0	1	3
	[67]	2001	Sweden	1958 - 1996	Retrospective	Cohort	Yes	P	-	17,438	6.9	72	-	-	4	2	1	7
	[55]	1992	USA	1980 - 1988	Retrospective	Cohort	No	H	Only those who had MMS	101	-	67	5	-	0	2	1	3
	[28]	1992	USA	1980 - 1989	Prospective	Cohort	No	H	Multi-center trial	189	-	-	5	-	0	2	1	3
	[13]	2004	Scotland	1999 - 2003	Retrospective	Cohort	No	H	-	104	21.2	77	4	-	0	1	1	2
	[17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	2,192	17.3	-	-	-	3	1	1	5
	[54]	2009	Australia	1996 - 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3	3
BCC after SCC	[60]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	6,401	5.2	74	4	-	4	1	3	8
(n=8)	[24]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	169	43.2	71	-	-	4	0	1	5
	[25]	2002	USA	1974 - 1989	Retrospective	Case - control	No	H	-	822	10.8	-	8	-	2	0	2	4
	[13]	2004	Scotland	1999 - 2003	Retrospective	Cohort	No	H	-	104	14.4	77	4	-	0	1	1	2
	[53]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	4,639	6.8	74	-	23,152	4	2	2	8
	[76]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-	-	2	0	1	3
	[17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	2,192	43.0	-	-	-	3	1	1	5
	[54]	2009	Australia	1996 - 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3	3
Melanoma	[60]	2009	Ireland	1993 - 2002	Retrospective	Cohort	Yes	P	-	6,401	0.2	74	4	-	4	1	3	8
after SCC	[24]	1990	USA	1976 - 1984	Retrospective	Cohort	No	P	-	169	1.8	71	-	-	4	0	1	5
(n=11)	[25]	2002	USA	1974 - 1997	Retrospective	Case - control	No	H	-	822	1.2	-	8	-	2	0	2	4
	[68]	1995	Denmark	1978 - 1989	Retrospective	Cohort	Yes	P	-	5,100	0.3	75	-	22,916	4	2	2	8
	[53]	1997	Switzerland	1974 - 1994	Retrospective	Cohort	Yes	P	-	4,639	0.5	74	-	23,152	4	2	2	8
	[69]	2005	UK	1961 - 2000	Retrospective	Cohort	Yes	P	-	25,731	0.3		-		4	1	1	6
	[20]	2005	Canada	1956 - 2000	Retrospective	Cohort	Yes	P	-	7,833	0.5	73	-	61,416	4	2	1	7
	[76]	2010	UK	1998 - 2007	Retrospective	Cohort	Yes	P	-	-	-	-	-		2	0	1	3

Supplemental Table 1. (continued)

	Reference number	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% subsequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
	[12]	2002	Bulgaria	1993 - 2000	Retrospective	Cohort	Yes	P	-	741	0.5	-	-	15,856	4	1	2	7
	[70]	1999	Sweden	1985 - 1992	Retrospective	Cohort	Yes	P	-	25,947	0.4	75	5	137,312	4	2	3	9
	[54]	2009	Australia	1996 - 2006	Retrospective	Cohort	No	H	-	40	-	65	8	-	0	0	3	3

C. Keratinocyte carcinoma (KC) as index tumor

	Reference number	Year	Country	Time period	Study design		Cancer registry	Hospital -(H) or population (P) -based	Subgroup	No. of patients	% subsequent tumor	Mean age (years)	Mean follow-up (years)	Person years (total)	NOS S	C	O	T
KC after KC	[26]	2002	Australia	1988 - 1989	Prospective	Cohort	No	H	-	481	67.8	-	10	-	0	1	2	3
(n= 8)	[29]	2004	Spain	1995 - 2001	Retrospective	Cohort	No	H	-	535	22.4	68	2	-	0	0	1	1
	[28]	1992	USA	1980 - 1989	Prospective	Cohort	No	H	Multi-center trial	1,805	-	-	5	-	0	2	1	3
	[27]	2002	Australia	1997 - 1999	Prospective	Cohort	No	P	-	6,708	38.5	-	-	-	2	0	1	3
	[71]	2001	USA	1996 - 1998	Retrospective	Cohort	No	H	96% on head and neck	440	39.3	-	2	-	1	0	2	3
	[17]	1990	USA	1985 - 1988	Retrospective	Cohort	Yes	P	-	6,310	50.0	69	-	-	3	1	1	5
	[72]	2001	Denmark	1995 - 1998	Prospective	Cohort	No	H	-	638	27.1	-	2	-	0	0	0	0
	[72]	2001	Denmark	1990 - 1993	Prospective	Cohort	No	H	-	526	20.3	-	2	-	0	0	0	0

Abbreviations: BCC, basal cell carcinoma; H, hospital-based; KC, keratinocyte carcinoma; N, number; NA, not applicable; NOS, Newcastle – Ottawa scale; P, Population-based; SCC, squamous cell carcinoma; SCOT, Selection Comparability Outcome Total NOS; USA, United States of America.

[a] The following information was extracted from each study: (1) study design; (2) in - and exclusion criteria of the study; (3) abstract or full text; (4) the number of followed patients with a (first) BCC, SCC or KC (the latter, when only combined data on BCC and SCC were available); (5) characteristics of study population (sex, mean [SD; standard deviation] or median age in years, mean [SD] or median follow-up time in years, total number of person-years); (6) risk estimate of developing a second or subsequent BCC, SCC, melanoma or KC (i.e. proportion, cumulative risk [CR], standardized incidence ratio [SIR]); (7) first cutaneous malignancy within patient (yes, no or unknown); (8) inclusion of in situ cutaneous malignancies (yes, no or unknown); (9) study location and continent; (10) year of publication.
In studies providing a CR for men and women separately without an overall CR, these numbers were averaged. Different nomenclature in medical literature is used for the risk measure 'Standardised Incidence Ratio' (SIR), therefore 'relative risk' (RR) and observed divided by expected (O:E) were also considered a SIR.

Supplemental Table 2. Search strategy and strings
See chapter 2 and http://www.sciencedirect.com/science/article/pii/S0959804913002128 .

Supplemental Table 3A. Adapted Newcastle – Ottawa quality assessment scale for cohort studies
See chapter 2 and http://www.sciencedirect.com/science/article/pii/S0959804913002128 .

Supplemental Table 3B. Adapted Newcastle – Ottawa quality assessment scale for case-control studies
See chapter 2 and http://www.sciencedirect.com/science/article/pii/S0959804913002128 .

Part I

Multiple

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CHAPTER 4

Risk of second primary in situ and invasive melanoma in Dutch population-based cohort: 1989 – 2008

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Br J Dermatol. 2012 Dec;167(6):1321-30.

SUMMARY

Background

Patients with melanoma are at increased risk of developing a subsequent melanoma.

Objectives

To estimate the risks of developing a second primary in situ or invasive cutaneous melanoma after a first melanoma, between 1989 and 2008.

Methods

Patients were followed until diagnosis of a second melanoma, date of death or end of study. Cumulative risks, standardized incidence ratio (SIR, observed second melanomas divided by background age-, calendar- and sex-specific incidence rates of melanoma, as recorded in the Netherlands Cancer Registry) and absolute excess risk (AER, observed minus expected per 10,000 person-years) of second melanomas were calculated.

Results

In total, 10 765 patients with in situ melanoma and 46 700 with invasive melanoma were included. Cumulative risks of a second invasive melanoma after a first in situ or invasive melanoma at 20 years of follow-up were 6.2% and 5.0%, respectively. Relative risk of developing any melanoma (in situ or invasive) after any first melanoma (SIR) was 12.4 [invasive after invasive melanoma; 95% Confidence Interval (CI) = 11.6–13.2] to 26.4 [in situ after in situ melanoma; 95% CI = 22.6–30.7] fold increased compared to the general population. SIRs and AERs remained elevated up to 20 years after the first melanoma.

Conclusions

This study shows significantly increased long-term risks (both relative and absolute) of developing a second invasive melanoma after a first melanoma (invasive and in situ), and might serve as a basis for follow-up guidelines.

Funding sources: This study is funded by the Dutch Cancer Society (KWF): The increasing burden of second primary cancers in the Netherlands: trend in incidence, survival and causes-of-death since 1970 (EMCR 2008-4132).

INTRODUCTION

The incidence rate of cutaneous melanoma (melanoma) in Europe has increased annually over the last 50 years.[1] In the Netherlands, the European standardized incidence rate has almost doubled between 1989 and 2008 from 11 per 100,000 person-years to 22 with an Estimated Annual Percentage Change of 4.1% (95% Confidence Interval: 3.6 – 4.5).[2] This rising trend has been reported previously in several studies[1,3-5], and is usually attributed to increased sun exposure in the general population, especially at young ages. The majority of melanomas are detected in early stages[2], when simple excision often results in cure. Consequentially, survival rates are relatively high (in the time period 2004-2008 the 10-year relative survival of melanoma in the Netherlands was 77% and 88% for males and females, respectively).[2] Thirty percent of melanoma patients report symptoms of psychological distress.[6] Second melanomas detected among melanoma patients who were not under active follow-up had a higher Breslow thickness compared with those in follow-up[7], suggesting a beneficial effect, although methodological difficulties in that study preclude an unequivocal conclusion.

The melanoma guideline in the Netherlands advises different follow-up schemes for cutaneous melanoma patients depending on Breslow thickness: patients with melanomas with a Breslow thickness of less than 1 millimeter (mm) require a single control visit, one month after treatment; those with 1 to 2 mm thickness are advised a follow-up time of 5 years and those with more than 2 mm thickness are advised to be in follow-up for 10 years (www.cbo.nl, accessed 1 February 2012; Guideline Melanoma of the skin, 2005). Internationally, follow-up guidelines vary considerably, from one control visit one month after treatment in the Netherlands, to lifelong annual follow-up visits for all stage I melanomas in Australia / New Zealand[8], which suggests a perception of the underlying risk. Follow-up schemes for in situ melanoma patients have not been formulated in the Dutch guideline.

In this study we investigated the risk pattern of second primary cutaneous melanomas among patients with melanoma (both invasive and in situ) in the Netherlands, by duration of follow-up, in order to provide information for optimal follow-up guidelines.

METHODS

Data

The population-based Netherlands Cancer Registry (NCR) provided incidence data of all patients diagnosed with in situ (International Classification of Diseases (ICD)-10 D.03) and invasive (ICD-10 C.43) cutaneous melanoma between 1989 and 2008. Information on vital status was obtained by linkage with the Dutch Municipality Register. Recurrence data were not collected. Detailed description of data has been described elsewhere.[2] The locations of the in situ and invasive melanomas were subdivided in the categories head and neck, trunk, arms, legs, other (including genital region) and unknown. The most common histopathological subtypes of melanoma were categorized as superficial spreading melanoma (SSM), nodular melanoma, acrolentiginous melanoma (ALM), lentigo maligna melanoma (LMM), lentigo maligna, melanoma in situ and other. Breslow thickness was categorized into 5 categories: lower than or equal to 1 mm, 1.01 – 2.0 mm, 2.01 – 4.0 mm, higher than 4 mm and unknown. The tumour stage was not used, as the criteria have changed repeatedly in the past.

Patient selection

Patients diagnosed with an either in situ or invasive cutaneous melanoma between 1989 and 2008 were included. Person-years at risk were calculated as time from first cancer diagnosis until the diagnosis of a second primary melanoma (for invasive and in situ, separately), date of death or end of follow-up (December 31 2008), whichever came first. It is of note that all the second melanomas were included. For instance, after a first melanoma diagnosis, if the second cancer is non-melanoma cancer and the third is melanoma, this melanoma is included, and so forth for other rank cancers. Patients were excluded if other invasive cancers were diagnosed before the first primary melanoma.

Statistical analysis

To analyze heterogeneity in characteristics (sex, tumour location, Breslow thickness and histopathological subtype) between first primary invasive melanomas and second primary melanomas the Chi-square test was used. The cumulative risk of second melanoma up to 20 years after diagnosis of the first melanoma was calculated taking the competing risks invasive cancers (other than melanoma) and death into account.[9] The standardized incidence ratio (SIR) is the ratio between the observed number of second melanomas and the expected number from the general population. It is a useful multiplicative measure for determining excess risk of second melanoma relative to the background risk in the general population. To derive the expected numbers, person-years under age-specific (5-year band), calendar-specific (1-year band) and sex-specific strata were multiplied with the corresponding background incidence rate from the general Dutch population. SIR >

1 indicates that the risk of developing a second melanoma is higher among melanoma patients than among the general population. Absolute excess risk (AER) is an additive measure for determining additional incidence beyond background incidence due to occurrence of a second melanoma. It is expressed as the difference between the observed number and the expected number per 10,000 person-years (i.e. (O-E) / person-years at risk x 10,000). Both SIR and AER were illustrated under follow-up periods of 0-1 year, 2-5 years, 6-10 years, 10-15 years and 16-20 years after the first melanoma diagnosis. The 95% CI was under Poisson distribution and the statistical significance level was estimated as two-sided at 0.05.

RESULTS

Cohort characteristics

Of the 57,465 patients with a first primary melanoma (10,765 in situ and 46,700 invasive conditions), 3.2% (n=1,840) developed a second primary melanoma between 1989 and 2008. The majority of second melanomas (71%) were invasive (n=1,301). Median follow-up time for in situ melanoma patients was 5.4 years (Interquartile range (IQR) = 2.3-9.9 years; male) and 6.1 years (IQR = 2.7-10.7 years; female) and for invasive melanoma patients 4.2 years (IQR = 1.7-8.9 years; male) and 5.6 years (IQR = 2.3-10.8 years; female).

Table 1 shows the characteristics of the first and second melanomas among the in situ and invasive melanoma patients with second primary melanomas. The median age of patients with a first in situ melanoma was 64 years (Interquartile range (IQR) = 52–74 years) and with a first invasive melanoma 52 years (IQR = 40–64 years). First in situ melanomas were most frequently (61%) located in the head or neck area, whereas first invasive melanomas were most frequently located on the trunk (36%). The most frequently occurring histopathological subtypes of the first and second invasive melanomas were SSM (57% and 67% respectively) and nodular melanoma (13% and 9%, respectively). First and second in situ melanomas were predominantly lentigo maligna (62% and 76%, respectively). On average, second melanomas were thinner than the first invasive melanomas (Table 1). In the majority of the cases second melanomas occurred in the first 5 years after the first melanoma diagnosis (Table 1). The differences in sex of patients with a second primary melanoma are shown in Supplementary Table 1 (Table S1).

Table 1. Characteristics of patients with second melanomas after a first in situ or invasive melanoma, 1989-2008

		1st *in situ* melanoma[a]				1st invasive melanoma[b]		
		n	%	Median age (yr) (IQR)		n	%	Median age (yr) (IQR)
Number patients with 2nd melanoma	Total	471	4.4	64 (52 - 74)		1,369	2.9	52 (40 - 64)
	Second in situ	173	36.7	70 (60 - 79)		366	26.7	60 (46 - 72)
	Second invasive	298	63.3	69 (55 - 78)		1,003	73.3	55 (43 - 66)
Site of 1st melanoma	Head	287	60.9	68 (61 - 77)		208	15.2	64 (50 - 75)
	Trunk	74	15.7	52 (42 - 63)		498	36.4	49 (39 - 60)
	Arms	56	11.9	53 (38 - 64)		285	20.8	54 (42 - 65)
	Legs	50	10.6	50 (35 - 67)		359	26.2	48 (36 - 60)
	unknown / other	4	0.8	67 (65 - 75)		19	1.4	55 (41 - 64)
Site of 2nd *in situ* melanoma	Head	118	68.2	73 (64 - 81)		104	28.4	72 (62 - 80)
	Trunk	11	6.4	60 (44 - 63)		98	26.8	54 (42 - 63)
	Arms	17	9.8	61 (52 - 71)		85	23.2	62 (49 - 73)
	Legs	25	14.5	55 (45 - 72)		78	21.3	50 (38 - 62)
	unknown / other	2	1.2	76 (75 - 77)		1	0.3	63 (63 - 63)
Site of 2nd invasive melanoma	Head	144	48.3	75 (67 - 82)		167	16.7	64 (48 - 77)
	Trunk	60	20.1	57 (45 - 68)		361	36.0	54 (43 - 63)
	Arms	41	13.8	67 (57 - 76)		216	21.5	56 (44 - 69)
	Legs	47	15.8	59 (43 - 71)		254	25.3	52 (41 - 63)
	unknown / other	6	2.0	51 (38 - 68)		5	0.5	65 (54 - 75)
Histopathological subtype 1st melanoma	NM[c]	1	0.2	73 (73 - 73)	NM	181	13.2	56 (41 - 66)
	SSM[c]	47	10.0	50 (36 - 63)	SSM	776	56.7	49 (38 - 60)
	LM	291	61.8	68 (61 - 77)	LMM	52	3.8	70 (62 - 78)
	MEL IN SITU	113	24.0	49 (40 - 63)	MM NOS	304	22.2	51 (41 - 65)
	ALM[c]	1	0.2	54 (54 - 54)	ALM	8	0.6	67 (59 - 78)
	other	18	3.8	70 (62 - 73)	other	48	3.5	60 (52 - 69)
Histopathological subtype 2nd *in situ* melanoma	SSM[c]	11	6.4	65 (54 - 77)	SSM[c]	29	7.9	56 (46 - 65)
	LM	131	75.7	73 (63 – 80)	LM	147	40.2	71 (59 - 78)
	MEL IN SITU	29	16.8	56 (44 - 68)	MEL IN SITU	185	50.5	51 (41 - 63)
	ALM[c]	1	0.6	67 (67 - 67)	ALM[c]	1	0.3	32 (32 - 32)
	other	1	0.6	52 (52 - 52)	other	4	1.1	70 (62 - 80)

Table 1 (continued)

		1st *in situ* melanoma[a]				1st invasive melanoma[b]		
		n	%	Median age (yr) (IQR)		n	%	Median age (yr) (IQR)
Histopathological subtype 2nd invasive melanoma	NM	29	9.7	72 (62 - 81)	NM	91	9.1	54 (40 - 69)
	SSM	134	45.0	62 (46 - 72)	SSM	667	66.5	54 (42 - 64)
	LMM	59	19.8	75 (64 - 80)	LMM	42	4.2	69 (62 - 79)
	MM NOS	59	19.8	68 (52 - 81)	MM NOS	164	16.4	54 (43 - 70)
	ALM	0	0.0	NA	ALM	4	0.4	59 (52 - 71)
	other	17	5.7	71 (69 - 78)	other	35	3.5	62 (55 - 74)
Breslow thickness 1st invasive melanoma[d]					≤ 1 mm	586	55.5	49 (39 - 61)
					1.01 - 2.0 mm	230	21.8	54 (46 - 66)
					2.01 - 4.0 mm	142	13.5	59 (46 - 70)
					> 4 mm	62	5.9	65 (56 - 72)
					Unknown	35	3.3	54 (40 - 73)
Breslow thickness 2nd invasive melanoma[d]	≤ 1mm	176	61.8	64 (49 - 75)	≤ 1mm	660	70.3	54 (43 - 65)
	1.01 - 2.0 mm	42	14.7	73 (59 - 82)	1.01 - 2.0 mm	160	17.0	56 (44 - 67)
	2.01 - 4.0 mm	34	11.9	77 (69 - 81)	2.01 - 4.0 mm	55	5.9	64 (51 - 77)
	> 4 mm	14	4.9	79 (67 - 93)	> 4 mm	34	3.6	72 (57 - 82)
	unknown	19	6.7	71 (63 - 80)	Unknown	30	3.2	57 (46 - 71)
Time to 2nd *in situ* melanoma	0 – 1 year	40	23.1	NA		134	36.6	NA
	2 – 5 years	75	43.4	NA		134	36.6	NA
	6 – 10 years	43	24.9	NA		61	16.7	NA
	11 – 14 years	12	6.9	NA		28	7.7	NA
	15 – 20 years	3	1.7	NA		9	2.5	NA
Time to 2nd invasive melanoma	0 – 1 year	53	17.8	NA		312	31.1	NA
	2 – 5 years	125	41.9	NA		347	34.6	NA
	6 – 10 years	74	24.8	NA		221	22.0	NA
	11 – 14 years	36	12.1	NA		94	9.4	NA
	15 – 20 years	10	3.4	NA		29	2.9	NA

Source: Netherlands Cancer Registry

[a] Total cohort of 10,765 in situ melanoma patients at risk; Person-years at risk 73,743; Median follow-up time males 5.4 years [IQR 2.3-9.9] and females 6.1 years [2.7-10.7]. [b] Total cohort of 46,700 invasive melanoma patients at risk; Person-years at risk 301,758; Median follow-up time males 4.2 years [IQR 1.7 - 8.9] and females 5.6 years [2.3 – 10.8]. [c] In situ melanoma with (erroneous) invasive morphology code. [d] Only Breslow thickness available in time period 1993 – 2008. Abbreviations: 'IQR'= Interquartile range, 'NM'= Nodular melanoma, 'SSM'= Superficial spreading melanoma, 'LM'= Lentigo Maligna, 'LMM'= Lentigo Maligna Melanoma, 'MEL IN SITU'= Melanoma in situ, 'MM NOS'= Malignant melanoma not otherwise specified, 'ALM'= Acrolentiginous melanoma, 'mm'= millimeter, 'NA'= not applicable.

Table 2. Comparison of tumour characteristics of the first invasive melanoma and a second primary invasive melanoma

	1st melanoma (n)[a]	%	2nd melanoma (n)	%	p-value[b] (degrees of freedom)
Sex					
Male	19,664	42.1	569	43.7	0.2407 (1)
Female	27,036	57.9	732	56.3	
Site of melanoma					
Head	5,866	12.6	311	23.9	<0.0001 (4)
Trunk	16,156	34.6	421	32.4	
Arms	8,865	19.0	257	19.8	
Legs	13,864	29.7	301	23.1	
unknown / other	1,949	4.2	11	0.9	
Histopathological subtype					
NM	6,546	14.0	120	9.2	<0.0001 (5)
SSM	25,576	54.8	801	61.6	
LMM	1,332	2.9	101	7.8	
MM NOS	10,999	23.6	223	17.1	
ALM	382	0.8	4	0.3	
other	1,865	4.0	52	4.0	
Breslow thickness					
≤ 1 mm	21,276	54.9	836	68.3	<0.0001 (4)
1.01 - 2.0 mm	7,952	20.5	202	16.5	
2.01 - 4.0 mm	5,061	13.0	89	7.3	
> 4 mm	3,111	8.0	48	3.9	
unknown	1,384	3.6	49	4.0	

Source: Netherlands Cancer Registry

[a]All first invasive melanomas in the database, regardless of occurrence of a second melanoma in the same patient. [b]Chi-square test. Abbreviations: 'SSM'= Superficial spreading melanoma, 'NM'= Nodular melanoma, 'LMM'= Lentigo Maligna Melanoma, 'ALM'= Acrolentiginous melanoma, 'mm'= millimeter.

In Table 2 the characteristics of the first and second invasive melanomas are compared. Patients' sex distributions of the first and the second primary melanomas were comparable. The localisation distribution differed significantly; second melanomas were more likely to occur in the head region than the first melanomas (24% vs. 13%, $p<0.0001$ with four degrees of freedom) as is confirmed by the significantly higher proportion of lentigo maligna melanoma (LMM) among the second melanomas (8% versus 3%). Second primary melanoma showed a higher frequency of superficial spreading melanoma (SSM) compared to the first melanoma (62% and 55% respectively, $p<0.0001$ with five degrees of freedom). The Breslow thickness of second melanomas was less than or equal to 2 mm in 85% of the cases compared to 75% in the first melanoma group.

Thick melanomas (>4 mm) were more common in the first invasive melanoma group (8% vs. 4%, p<0.0001 with four degrees of freedom).

Cumulative risk

The 5-year cumulative risk of getting a second invasive melanoma after a first in situ or first invasive melanoma was 2.1% and 1.8%, respectively, 10-year cumulative risk was 3.7% and 3.0%, 15-year cumulative risk was 5.2% and 4.0% and 20-year cumulative risk was 6.2% and 5.0%. The cumulative risk of developing a second primary in situ or invasive melanoma increased constantly with follow-up time (follow-up time 0–20 years) (Figure 1). Cumulative risk of an invasive melanoma after a first invasive melanoma was consistently higher for females than for males (Figure 2).

Standardized incidence ratio (SIR) and Absolute excess risk (AER)

SIRs of developing a second primary melanoma after a first melanoma were highest in the first year after the first melanoma diagnosis for all groups (SIRs 16.5 [95% CI = 11.0 – 24.0] – 53.7 [95% CI = 40.2 – 70.4]) but remained elevated up to 20 years after the first melanoma diagnosis (Table 3). Patients with an in situ melanoma were at increased risk of developing a second in situ melanoma (SIR 26.4 [95% CI = 22.6 – 30.7]) or second invasive melanoma compared to the general population (SIR 15.4 [13.7 – 17.3]). SIR of an invasive melanoma after an invasive melanoma was 12.4 [11.6 – 13.2] and SIRs of this group were consistently higher for male patients compared to female patients, regardless of time since diagnosis. AERs were highest in the first year after the first melanoma and decreased over follow-up time. The AERs of an invasive melanoma after a first invasive melanoma were 36.4 / 10,000 (males) and 27.0 / 10,000 (females) person-years, and after a first in situ melanoma 44.0 / 10,000 (males) and 34.4 / 10,000 (females) person-years (Table 3).

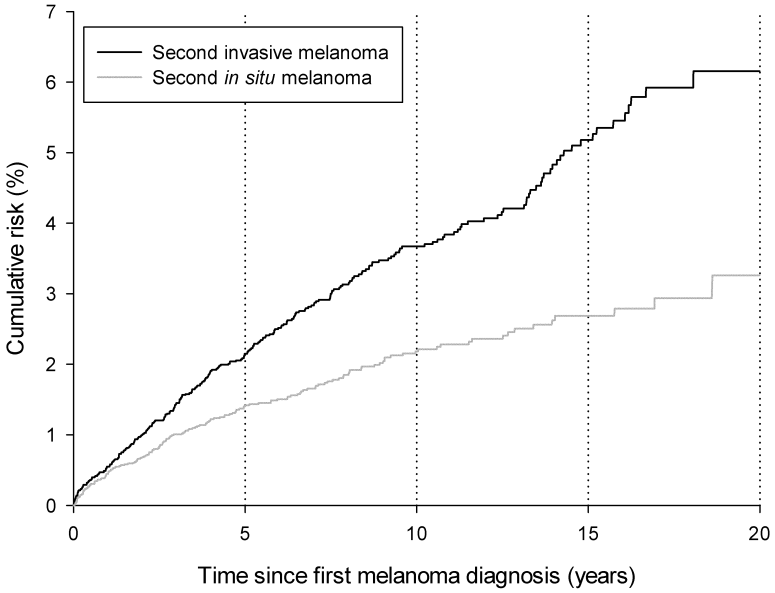

Figure 1(a). Cumulative risk of second melanomas after a first in situ melanoma

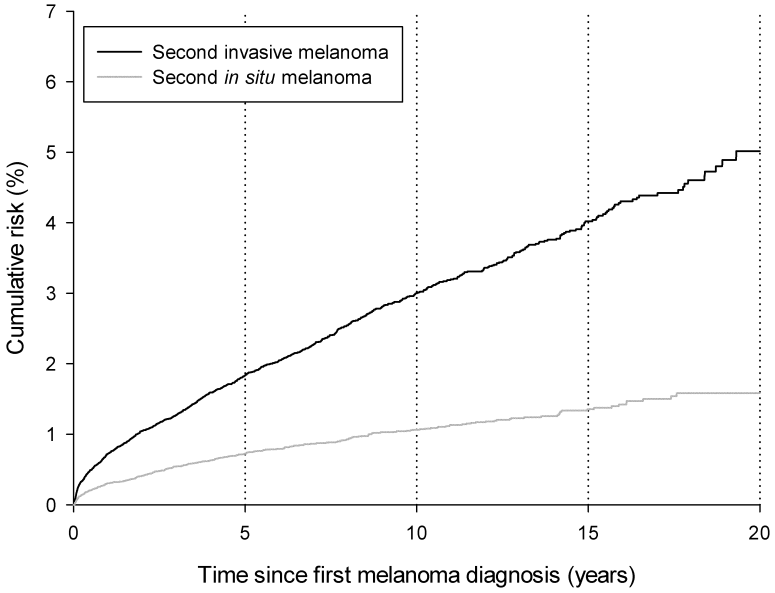

Figure 1(b). Cumulative risk of second melanomas after a first invasive melanoma

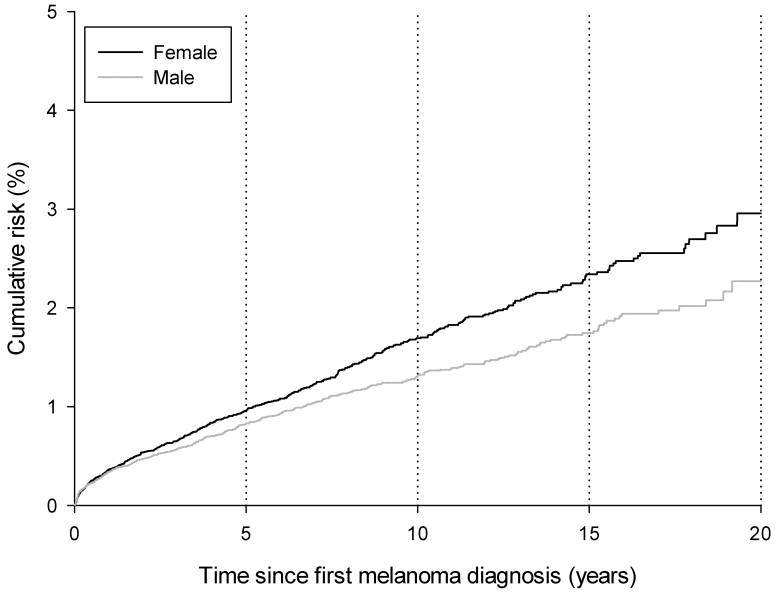

Figure 2. Cumulative risk of second invasive melanomas in male and female patients with invasive melanomas

DISCUSSION

This large, population based study investigating risks of developing second melanomas in cohorts of patients with both in situ and invasive melanoma showed markedly increased total relative (12 to 26 fold) and absolute risks (11 to 38 per 10,000 person-years). These risks remained increased for more than 15 years after the first diagnosis of melanoma.

In our data, 2.1% of patients developed a second primary invasive melanoma after a first invasive melanoma and the average 20-year cumulative risk was 5.6%. Internationally, considerable variations in incidence figures of a second melanoma after a first melanoma (range proportions: 1.0% - 4.4% and cumulative risks: 5.0% - 8.1%) have been reported (Table 4).[10-16] The SIRs in the Netherlands were high compared to relative risks reported in other countries which varied from 3.4 [95% CI = 1.9 – 5.6] to 38.5 [95% CI = 30.4 – 48.1] (Table 4).[10-15,17] Explanations should be sought in underlying incidence rates (shared risk factors or detection), chance of survival after the first cancer[18] or diagnostic bias / misclassification. Besides, as the SIR is a ratio of incidence rates in the cohort under study and the background population, the level of SIR will be strongly influenced by background incidence rates, the high background incidence rates in Australia may explain the lower SIR from Victoria, Australia.[11] A German study showed a high SIR of up to 38.5[13], probably

Table 3. Standardized Incidence Ratio (SIR and 95% confidence intervals) and Absolute Excess Risk (AER, per 10,000 person-years) of second primary melanomas after melanomas in different follow-up periods

Second *in situ* melanoma after first *in situ* melanoma								**Second *in situ* melanoma after first invasive melanoma**							
	Follow-up period	O	E	SIR	95% CI	PY at risk	AER		Follow-up period	O	E	SIR	95% CI	PY at risk	AER
Male	0 - 1 year	13	0.3	45.5	24.2 - 78.9	3,744.9	11.5	**Male**	0 - 1 year	53	1.0	53.7	40.2 - 70.4	18,018.7	28.9
	2 - 5 years	20	0.9	23.2	14.1 - 36.1	11,068.6	25.7		2 - 5 years	45	2.8	16.1	11.7 - 21.6	48,736.2	8.7
	6 - 10 years	14	0.6	21.7	11.9 - 37.0	7,451.0	49.9		6 - 10 years	20	2.0	10.1	6.2 - 15.7	30,947.5	5.8
	11 - 14 years	2	0.3	7.8	0.9 - 32.7	2,678.3	16.7		11 - 14 years	11	0.9	12.6	6.3 - 22.9	11,920.6	8.5
	15 - 20 years	0	0.1	0.0	NA	1,045.1	-1.1		15 - 20 years	2	0.5	4.3	0.5 - 17.8	5,228.9	2.9
	Total	49	2.2	22.7	16.8 - 30.1	25,988.0	18.0		Total	131	7.1	18.4	15.4 - 21.9	114,851.7	10.8
Female	0 - 1 year	27	0.5	50.3	33.1 - 73.6	6,338.9	41.7	**Female**	0 - 1 year	81	1.7	47.9	38.0 - 59.6	25,288.7	31.4
	2 - 5 years	55	1.7	32.3	24.4 - 42.2	19,675.2	27.1		2 - 5 years	89	5.3	16.8	13.5 - 20.6	75,120.0	11.1
	6 - 10 years	29	1.3	21.8	14.6 - 31.5	14,022.7	19.7		6 - 10 years	41	4.3	9.6	6.9 - 13.0	53,792.5	6.8
	11 - 14 years	10	0.6	17.9	8.5 - 33.6	5,417.0	17.4		11 - 14 years	17	2.0	8.4	4.9 - 13.5	22,216.8	6.7
	15 - 20 years	3	0.3	11.5	2.3 - 36.7	2,301.2	11.9		15 - 20 years	7	1.1	6.3	2.5 - 13.5	10,488.0	5.6
	Total	124	4.4	28.3	23.5 - 33.7	47,755.0	25.0		Total	235	14.4	16.3	14.3 - 18.5	186,906.0	11.8
Total		173	6.5	26.4	22.6 - 30.7	73,743.0	22.6	**Total**		366	21.5	17.0	15.3 - 18.8	301,757.7	11.4

Table 3 (continued)

Second invasive melanoma after first *in situ* melanoma								Second invasive melanoma after first invasive melanoma							
	Follow-up period	O	E	SIR	95% CI	PY at risk	AER		Follow-up period	O	E	SIR	95% CI	PY at risk	AER
Male	0 - 1 year	25	1.0	25.2	16.3 - 37.4	3,744.9	64.1	**Male**	0 - 1 year	151	4.2	36.0	30.5 - 42.3	18,018.7	81.5
	2 - 5 years	49	3.0	16.1	11.9 - 21.3	11,068.6	41.5		2 - 5 years	155	11.7	13.2	11.2 - 15.5	48,736.2	29.4
	6 - 10 years	26	2.2	11.6	7.6 - 17.1	7,451.0	31.9		6 - 10 years	89	8.2	10.9	8.7 - 13.4	30,947.5	26.1
	11 - 14 years	19	0.9	21.5	12.9 - 33.8	2,678.3	67.6		11 - 14 years	38	3.6	10.7	7.5 - 14.7	11,920.6	28.9
	15 - 20 years	3	0.4	8.0	1.6 - 25.7	1,045.1	25.1		15 - 20 years	14	1.8	7.8	4.3 - 13.3	5,228.9	23.4
	Total	122	7.5	16.2	13.4 - 19.3	25,988.0	44.0		Total	447	29.4	15.2	13.8 - 16.7	114,851.7	36.4
Female	0 - 1 year	28	1.7	16.5	11.0 - 24.0	6,338.9	41.5	**Female**	0 - 1 year	161	6.3	25.4	21.7 - 29.7	25,288.7	61.2
	2 - 5 years	76	3.4	22.4	17.6 - 28.0	19,675.2	36.9		2 - 5 years	192	19.4	9.9	8.6 - 11.4	75,120.0	23.0
	6 - 10 years	48	4.1	11.6	8.6 - 15.4	14,022.7	31.3		6 - 10 years	132	15.2	8.7	7.3 - 10.3	53,792.5	21.7
	11 - 14 years	17	1.7	9.8	5.7 - 15.8	5,417.0	28.2		11 - 14 years	56	6.9	8.1	6.1 - 10.5	22,216.8	22.1
	15 - 20 years	7	0.8	8.6	3.5 - 18.4	2,301.2	26.9		15 - 20 years	15	3.6	4.1	2.3 - 6.9	10,488.0	10.8
	Total	176	11.8	14.9	12.8 - 17.3	47,755.0	34.4		Total	556	51.4	10.8	9.9 - 11.7	186,906.0	27.0
Total		298	19.3	15.4	13.7 - 17.3	73,743.0	37.8	**Total**		1,003	80.9	12.4	11.6 - 13.2	301,757.7	30.6

Source: Netherlands Cancer Registry

Abbreviations: 'O'= Observed number of cases, 'E'= Expected number of cases, 'SIR'=Standardized Incidence Ratio, '95% CI'=95% Confidence Intervals, 'PY'= Person-years, 'AER'= Absolute Excess Risk per 10,000 person-years, 'NA'= Not applicable.

caused by high numbers of second melanomas detected in a selected hospital-based study population which were divided by cancer registry background incidence rates. Finally, estimates will be influenced by the length of follow-up and degree of completeness of the cancer registry.[19] The Netherlands Cancer Registry is assumed to be 98.3% complete.[20] At this moment only two studies have calculated SIRs after a first in situ melanoma in which increased risks for more than 10 years after the first in situ melanoma were reported as well.[10,15] However, the Swedish data were relatively old and the sample size was low. AER was calculated in two previous studies and our findings are in agreement with theirs.[10,21]

A high incidence of melanoma in a group of melanoma patients might be related to high risk factor exposure, but also to increased patients' and doctors' awareness, diagnostic bias or registry artefacts. Slowly growing tumours are more likely to be discovered through this mechanism, illustrating length-time bias.[19,22] Previous studies observed high relative risks of developing a second melanoma related to fair skin type, presence of many or atypical moles and family history / genetic susceptibility of the melanoma patients, and modestly increased risks for patients whose first melanoma was an in situ / lentigo maligna or invasive melanoma[23-25] suggesting biologically increased risks. The NCR does not have information on risk factors like phototype or sun exposure and therefore we performed univariate analysis for age, sex, histopathological subtype, Breslow thickness and tumour location to predict occurrence of second melanomas, however, none of the above-listed factors yielded statistical significance (data not shown).

The histological interpretation of very small and difficult to interpret melanocytic lesions from patients with a history of melanoma is likely to result in some melanoma overdiagnosis, and in enrichment of the total group of second primary melanomas with exceedingly small and thin lesions that have been inappropriately labelled as melanoma. Benign lesions that are misclassified as melanoma could be a cause of, or contribute to, the melanoma 'epidemic'.[26-28] A recent paper stated that follow-up visits are an effective method to increase early detection of melanoma.[7] However, the second melanomas in the follow-up group of this study were extremely thin (mean Breslow thickness: 0.36 mm) or melanomas in situ, and could indeed have included overdiagnosed small melanoma simulators. So, intensive follow-up visits might increase the risk of an inappropriate additional diagnosis of melanoma. Indications for the occurrence of this phenomenon are also present in our data (Table 1); we found that the majority of the second melanomas were found in the first 5 years after the first melanoma diagnosis when the most follow-up visits are scheduled. However, whether or not patients follow the Dutch guideline follow-up visit scheme in our study is unknown.

Women could be at increased risk (Figure 2) of developing second melanomas compared to males because of higher awareness. This increased risk could also correspond to the

higher incidence of primary melanoma in women in most European countries[5] and the better survival of women with melanoma[29-30] allowing women more time to develop a subsequent melanoma.

The increased risk of developing a second primary melanoma up to 20 years after the first melanoma diagnosis might be an indication for more extensive follow-up programs, although the effectiveness of follow-up programs in improving prognosis is controversial.[8,31-32] Analyses on potential differences in survival of the group of multiple melanoma patients versus the group with only one melanoma could give further information on the prognostic importance of the diagnosis of a second melanoma. This data may shed light on importance of increased surveillance of patients with a first primary melanoma.

Currently, there is not enough available evidence to prove efficacy of skin cancer screening.[33-35] Selecting and examining high-risk populations (for melanoma e.g., genodermatosis including Familial Atypical Mole - Malignant Melanoma (FAMMM) syndrome) and performing full body skin examination of people visiting physicians (i.e., 'case finding' by clinicians) might be the best strategy to decrease the burden of skin cancer.[34] Education of nurses or physiotherapists could also be an important method to improve early detection[36], but large studies are lacking.

In addition to disease progression and psychological support, follow-up visits suggested by malignant melanoma guidelines should include total body skin examinations to exclude second primary melanoma, because this patient group is at a highly increased risk. A SIR greater than 10.0 with an AER of more than 5.0 per 10,000 person-years is, in our opinion, large enough to conclude that a history of either an in situ or invasive melanoma is a strong risk indicator for detection of subsequent invasive melanomas and that both in situ and invasive melanoma patients must be considered to be at high risk and patient education and full body skin examinations should be performed during follow-up visits. Since the excess risk is persistent in time (up to 20 years), the duration of current follow-up recommendations for this indication remains debatable. A melanoma follow-up study found a relatively low delay in diagnosis when a follow-up schedule with lower frequency than current guidelines was used.[37] However, large randomized controlled trials investigating duration and frequency of follow-up visits and follow-up procedures are suggested.

In conclusion, the risk of developing a second primary melanoma is elevated for at least 20 years after the first melanoma diagnosis. The explanation of this increased risk is multifactorial and includes genetic predisposition, shared environmental risk factors and overdiagnosis. Nevertheless, patients and physicians need to be aware of the high and persistent risk of developing second primary melanomas.

Table 4. Recent studies reporting risks (proportion, cumulative risk and Standardized Incidence Ratio (SIR)) of developing a second primary melanoma after a first melanoma

Reference	Time-period		1st melanoma (n)	2nd melanoma (n)	Cumulative risk	Person-years at risk	Age 1st melanoma (years)	Follow-Up (years)	Total SIR (95%CI)[b]	Follow-up SIR (years)[b]				
Balamurugan 2011 United States[10]	**1992 - 2006**		***In situ***	**Invasive**				**mean**	[a]	**0-0.1[a]**	**0.1-1[a]**	**1-5[a]**	**5-10[a]**	**>10[a]**
		Male	22,013	812 (3.7%)					8.4*	36.3*	9.9*	7.4*	7.3*	7.5*
		Female	18,868	438 (2.3%)					12.3*	77.2*	16.2*	10.0*	9.9*	7.2*
		Total	40,881	1,250 (3.1%)				5.6						
			Invasive	**Invasive**				**mean**		**0-0.1**	**0.1-1**	**1-5**	**5-10**	**>10**
		Male	41,715	1,850 (4.4%)					12.5*	102.1*	16.8*	9.9*	8.5*	6.2*
		Female	34,326	957 (2.8%)					15.7*	127.6*	22.1*	13.0*	9.9*	9.2*
		Total	76,041	2,807 (3.7%)				5.6						
Karahalios 2009 Australia[11]	**1982 - 2005**		**Invasive**	**Invasive**	**23 years**		**mean**	**mean**		**0-1**	**1-5**	**5-10**	**10-15**	**15-23**
		Male	14,241		8.1%	100,188	57	7.0	7.3 (6.7 - 7.8)	10.7*	8.1*	6.2*	5.7*	5.0*
		Female	14,011		6.2%	116,375	55	8.3	7.2 (6.6 - 7.9)	9.6*	8.5*	5.9*	6.4*	5.9*
		Total	28,252											
Cantwell 2009 Northern Ireland[17]	**1993 - 2002**		**Invasive**	**Invasive**			**mean**							
		Male					57							
		Female					55							
		Total	1,839						4.8 (1.2 - 8.3)					
Levi 2005 Switzerland[12]	**1974 - 2003**		**Invasive**	**Invasive**	**20 years**		**median**							
		Male	1,571	15 (1.0%)					3.4 (1.9 - 5.6)					
		Female	1,868	28 (1.5%)					5.7 (3.8 - 8.3)					
		Total	3,439	43 (1.3%)	5.0%	24,930	57		4.6 (3.4 - 6.2)					
Schmid-Wendtner 2001 Germany[13]	**1977 - 1992**		**Invasive**	**Invasive**				**median**	**SIR within 10 years[c]**					
		Male	2,083						38.5 (30.4 – 48.1)					
		Female	2,514						29.0 (22.0 – 37.5)					
		Total	4,597	152 (3.3%)				7.2	33.8 (28.3 – 39.9)					

Table 4 (continued)

Reference	Time-period		1st melanoma (n)	2nd melanoma (n)	Cumulative risk	Person-years at risk	Age 1st melanoma (years)	Follow-Up (years)	Total SIR (95%CI)[b]	Follow-up SIR (years)[b]				
Dong 2001 Sweden[14]	**1958 - 1996**		**Invasive**	**Invasive**			**median**	**median**		**0-1**	**0-9**	**1-9**	**10-38**	
		Male	10,704	195 (1.8%)		81,758	55	5.0			9.5*		5.7*	
		Female	11,460	170 (1.5%)		107,767	50	7.0			7.9*		6.5*	
		Total	22,164	365 (1.6%)						16.0*		8.0*	6.1*	
Wassberg 1999 Sweden[15]	**1958 - 1992**		***In situ***	**Invasive**			**mean**	**mean**	[a]	**0-1[a]**	**1-4[a]**	**5-9[a]**	**10-14[a]**	**>15[a]**
		Male	1,542	51 (3.3%)					23.8 (17.7 – 31.3)					
		Female	2,224	57 (2.6%)					20.9 (15.8 – 27.1)					
		Total	3,766	108 (2.9%)		20,038	56	5.3	22.2 (18.2 – 26.8)	28.2*	22.5*	19.4*	25.0*	7.4
Burden 1994 Scotland[16]	**1979 - 1991**		**Invasive**	**Invasive**										
		Male												
		Female												
		Total	3,818	45 (1.2%)										
Current study 2011 The Netherlands Source: NCR	**1989 - 2008**		***In situ***	**Invasive**	**20 years**		**median**	**median**	[a]	**0-1[a]**	**2-5[a]**	**6-10[a]**	**11-14[a]**	**15-20[a]**
		Male	4,005	122 (3.0%)			64	5.4	16.2 (13.4 – 19.3)	25.2*	16.1*	11.6*	21.5*	8.0*
		Female	6,760	176 (2.6%)			64	6.1	14.9 (12.8 – 17.3)	16.5*	22.4*	11.6*	9.8*	8.6*
		Total	10,765	298 (2.8%)	6.2%	73,743	64		15.4 (13.7 – 17.3)					
			Invasive	**Invasive**			**median**	**median**		**0-1**	**2-5**	**6-10**	**11-14**	**15-20**
		Male	19,664	447 (2.3%)			55	4.2	15.2 (13.8 – 16.7)	36.0*	13.2*	10.9*	10.7*	7.8*
		Female	27,036	556 (2.1%)			49	5.6	10.8 (9.9 – 11.7)	25.4*	9.9*	8.7*	8.1*	4.1*
		Total	46,700	1,003 (2.1%)	5.0%	301,758	52		12.4 (11.6 – 13.2)					

[a]SIR invasive melanoma after first in situ melanoma. [b]All SIRs reported were statistically significant increased. [c]in situ melanomas included in analysis. *SIR differs significantly from 1 ($p < 0.05$). Abbreviations: 'NCR'= Netherlands Cancer Registry, 'CI'= Confidence Intervals, 'SIR'= Standardized Incidence Ratio.

ACKNOWLEDGEMENTS

The authors thank the registration teams of the Comprehensive Cancer Centres for the collection of data for the Netherlands Cancer Registry and the scientific staff of the Netherlands Cancer Registry. Grant sponsor: Dutch Cancer Society; Grant number: EMCR 2008-4132.

SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of male and female patients with second melanomas after a first in situ or invasive melanoma, 1989-2008

See http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2012.11123.x/suppinfo.

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Screening for second primary melanomas: is it efficient? Reply from authors

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Br J Dermatol. 2013 May;168(5):1135.

MADAM, Geurts et al[1] estimated the expected impact of prolonged follow-up of patients with a history of invasive melanoma on health care services. They concluded that extension of the follow-up period will result in overdiagnosis, overtreatment, anxiety in patients and a tripled workload for dermatologists. We agree that prolonged follow-up may have negative side effects and associated costs. However, purely from the perspective of secondary tumours there does not seem to be an upper limit of follow-up time after which the incidence decreases.

Reasons for follow-up of patients with melanoma include detection of a recurrence, diagnosis of second primary melanomas (and other cutaneous malignancies) and psychosocial support / information provision. The majority of recurrences and second primary melanomas are found in the first 5 years after the first melanoma diagnosis. The risk of recurrences decreases rapidly after the first 5 years of follow-up[2], but our results showed that the risk of a second primary melanoma remains constantly increased for at least 20 years in both in situ and invasive melanoma patients (probably lifelong).[3]

The new Dutch melanoma guideline is quite conservative and recommends melanoma patients to come back once one month after treatment of the primary melanoma combined with instructions for self-diagnosis (stage IA) and up to 5 years after diagnosis of the first melanoma (≥stage IB).[4] Studies concerning self-diagnosis showed that first recurrences of melanoma are most often detected by the patients themselves (76%).[5] The ability to auto-detect thin second primary melanomas seemed to be more difficult in patients with a history of melanoma (46%).[6] The 5-year follow-up period after a primary melanoma is generally accepted by clinicians. However, the patients' perspective has not been included in determining this cut off.

Geurts et al[1] pointed to potential negative psychosocial consequences for the patients with melanoma, but did not mention the fact that a proportion of the patients with melanoma find it re-assuring to have full body skin examinations more often than strictly recommended, as shown in a recent Dutch population based survey. This survey showed that almost 80% of patients with a melanoma Breslow thickness of less than 1 mm reported more follow-up visits than the guideline recommended and also patients with thicker melanomas showed "overconsumption" of health care.[7] This overconsumption (from the perspective of the physician and health care policy maker) may be due to patients asking for additional information about different aspects of melanoma[8] or another full body skin examination, and to a lesser extent due to physicians' preference.

In our opinion the duration and frequency of follow-up visits remain debatable and more research is needed to clarify the influence of follow-up visit schemes on melanoma survival and quality of life of melanoma survivors.

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Part I

Multiple

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CHAPTER 5

Risks of different skin tumor combinations after a first melanoma, squamous cell carcinoma and basal cell carcinoma in Dutch population based cohorts: 1989 – 2009

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Part I

Multiple

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CHAPTER 6

Cohort studies (and skin cancer) never come alone

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J Invest Dermatol. 2015 Mar;135(3):649-51.

ABSTRACT

A previous keratinocyte carcinoma is probably the strongest predictor of developing new keratinocyte carcinomas, which makes these patients an interesting population for prevention interventions. Investing in large cohort studies and consortia might increase the validity of observational findings and should stimulate scientists to investigate the underlying mechanisms in detail.

It is well known that the risk of a subsequent cutaneous malignancy is increased in patients with a previous keratinocyte carcinoma (KC). A recent meta-analysis showed that 29% of patients with a history of basal cell carcinoma (BCC) developed a subsequent BCC and 4% a subsequent squamous cell carcinoma (SCC), whereas 13% of patients with a history of SCC developed a subsequent SCC and 16% a subsequent BCC[1]. The majority of studies on multiple cutaneous malignancies calculated risks of a subsequent or second primary skin cancer but did not calculate risks of additional skin cancers. In this issue, Adèle Green's research group selected a cohort of 1,191 white-skinned Australian residents from their Nambour skin cancer prevention trial, without KC, before or at the start of this trial, to determine the proportion who developed a BCC exclusively, SCC, or both[2]. The original cohort consisted of 1,621 residents of the subtropical city Nambour, who were selected at random in 1986, and therefore the cohort reflects a general population sample from Australia followed prospectively between 1992 and 2007. Besides the type of skin cancer, the investigators also assessed anatomic site distributions and other clinical features such as pigmentary characteristics and signs of actinic damage. This study demonstrated that about 21% of the study population developed a first KC and 47% of this group developed at least a second KC. The majority of this latter group developed exclusively BCCs (56%), 28% developed both, and 16% developed SCCs exclusively, with age as the most important predictor of increasing incidence rates[2]. Participants who developed SCC exclusively were the most distinct group, because they had significantly higher prevalences of easily sunburned skin, propensity to tan without burning, and freckling of the back than did the BCC only and mixed groups. The skin, eye, and hair color characteristics showed no significant differences among the three groups. In those with BCCs exclusively or both BCC and SCC, the head and neck area were the predominant sites of development, whereas in the SCC only group the limbs were the predominant sites of development. These differences may be the result of differences in UVR exposure or genetic susceptibilities, and they suggest different tumor biologies.

Major strengths of this study are 16 years of follow-up, a clear case definition (i.e., histopathologically confirmed tumors), full-body skin examinations, and detailed information on clinical features. However, the main limitation lies in the small sample of patients with multiple cutaneous malignancies, especially the group who developed SCCs exclusively (n=28). Small sample sizes result in wide confidence intervals and a possible type II error (i.e., no power calculation shown). Although the cohort was followed for 16 years, the study population was young (mean age 46 years) at enrollment, suggesting that the majority of the patients had not yet reached the age in which the incidence of cutaneous malignancy is highest.

ACTINIC NEOPLASIA SYNDROME

Martin Weinstock coined the term "actinic neoplasia syndrome" to emphasize that cutaneous (pre-)malignancies are not a single event but often reflect a field dysplasia from which patients suffer chronically[3]. After the 1992 landmark study on this subject[4], many observational studies of different populations demonstrated that almost half of patients with cutaneous malignancy will develop at least a second KC, and even more will show other signs of chronic actinic skin damage (e.g., actinic keratosis, solar elastosis) due to the relatively high levels of acute, intermittent, and/or cumulative UVR exposure during their lives. Therefore, a previous cutaneous malignancy is probably the strongest predictor of developing subsequent malignancies, making this an interesting population for studies of prevention intervention. One might argue that the occurrence of multiple malignancies might pose a greater problem to both patients and health-care systems compared with disease progression or recurrence.

The benefits of primary prevention programs should become evident only after decades[5]. Even though people become more and more aware of the harmful effects of UVR, they do not seem to change their attitude toward it (i.e., knowledge–behavior gap[6]). For now, it seems that primary prevention is not meeting its expectations, as the incidence of skin cancer continues to increase worldwide, with the possible exception of Australia, which has a highly active public education campaign[7]. As primary prevention falls short, secondary prevention offers a good alternative strategy. This prevention method will be most successful when high-risk populations are defined and screening strategies for specific patient groups constructed. Well-calibrated, discriminating, and validated prediction models could provide physicians with a tool to find high-risk patients, such as patients with histories of skin cancer, and give them appropriate right follow-up and tailored instructions. If there indeed exists a type-specific skin cancer susceptibility, as suggested by Keim et al[2], different prediction models should be developed, combining environmental, phenotypic, and genotypic risk factors. However, there also exists a significant group of patients who develop both BCCs and SCCs, which is not surprising, as they share many risk factors (Figure 1). Although the risk factor profiles of the different cutaneous (pre-)malignancies are well documented, the extent to which these risk factors are applicable to subsequent tumors is not certain. On the basis of Rothman's sufficient-component cause model, it could be argued that the contribution of the conventional risk factors for a first event is not applicable to subsequent events, defined as the index event bias[8]. In recent decades, huge steps have been made in understanding the genetic predisposition (germline and somatic mutations) for BCC and to a lesser extent for SCC and actinic keratosis. However, our genetic understanding of these very common keratinocyte malignancies lags behind melanoma. Except for a few candidate gene studies and a genome-wide association study, no studies have investi-

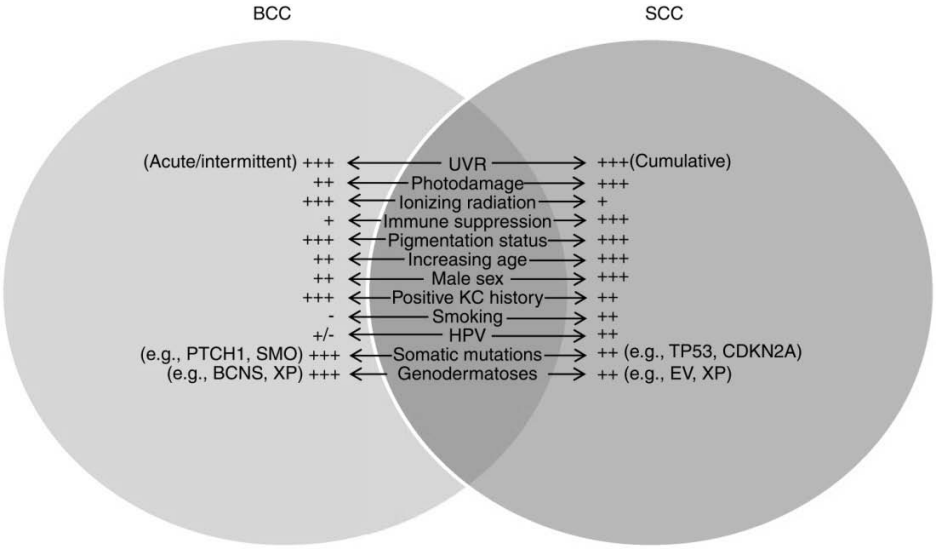

Figure 1. Risk factor profiles of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).
Abbreviations: BCNS, basal cell nevus syndrome; EV, epidermodysplasia verruciformis; XP, xeroderma pigmentosum.

gated the common or rare genetic variants found in patients with multiple keratinocyte malignanies. There is hope, because an international consortium has been established to explore the genetics of patients with multiple skin cancers and to develop prediction models that include genetic variation.

PROSPECTIVE FOLLOW-UP STUDIES

As dermato-epidemiologists, we noticed another important element in this study[2], which is the enormous return on investment seen in this prospective Nambour skin cancer study. Clinical epidemiology includes experimental and observational research that might aid our understanding of diseases through a quantitative approach of clinical problems. The Nambour skin cancer trial started as an experimental study (a randomized field trial) but extended its follow-up as a prospective cohort study. The advantages of that type of design are the possibility of calculating risk measures (absolute and relative risk) and a relatively low risk of bias compared with other observational designs. The classical argument against cohort studies is that they are too expensive, but large (population-based) prospective cohort studies such as the Nambour Skin Cancer Study, the Rotterdam Study, Nurses' Health Study, the Health Professionals Follow-up Study, and the PUVA Follow-up Study have a tremendous scientific return on investment in

many diseases, including skin cancer[2,9-11]. We are strong advocates of investing in well-designed and large cohort studies (including drug or disease specific registries), but at the same time we encourage investigators to form a consortia to increase sample size and to replicate each other's findings. Collaborative efforts increase the validity of the observational findings and should stimulate laboratory scientists even more strongly to investigate the underlying mechanisms in detail.

In conclusion, good research raises more questions than it answers, and it lifts the bar for scientific progress.

CLINICAL RELEVANCE:

- Development of multiple skin cancers may indicate the beginning of chronic disease.
- Basal cell carcinoma and squamous cell carcinoma do have risk factors in common, but they are distinct entities.
- Mechanistic studies will offer better understanding of the etiopathogenesis of skin cancer.

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Part II

Early / Pre

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CHAPTER 7

Time trends of thin melanomas in The Netherlands, 1994 – 2010

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Part II

Early / Pre

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CHAPTER 8

Prevalence of actinic keratosis and its risk factors in the general population: The Rotterdam Study

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J Invest Dermatol. 2013 Aug;133(8):1971-8.

ABSTRACT

Background

Actinic keratoses (AKs) are precursors of cutaneous squamous cell carcinomas (SCC). Limited data are available on the prevalence and risk factors of AK.

Methods

Within the Rotterdam Study, a Dutch population-based cohort study, full body skin examinations were performed among participants aged 45 years or older to estimate the age- and sex standardized prevalence of AK and its associated risk factors. A multinomial logistic regression model calculated adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for associations between risk factors and the presence of 1 – 3, 4 – 9 and ≥ 10 AK. Binary logistic regression compared participants without or with extensive actinic damage (≤ 9 AK versus ≥ 10 AK). By linking the participants to PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands, participants with a history of cutaneous malignancy were identified.

Results

Of the 2,061 inspected cohort members (mean age 72 years), 21% had 1 to 3, 9% 4 to 9 and 8% ten or more AK. Prevalence of AK in the Rotterdam Study was 49% (95% CI 46%–52%) for men and 28% (26%–31%) for women. Extrapolation suggested that approximately 1.4 of the 16 million Dutch citizens are affected with AK. Male sex, older age, light pigmentation status, severe baldness, skin wrinkling and high tendency for sunburn were significantly associated with number of AKs and extensive actinic damage (≥10 AKs) in the multivariate analyses. Especially bald males were at an increased risk of severe actinic skin damage (adjusted OR= 7.0 [3.8 – 13.1]). The group with no AKs had a lower positive history for SCC than the group with 10 AKs (1.2% and 13.6%, respectively).

Conclusions

The prevalence of AK is very high, especially among elderly bald males, and the presence of severe actinic damage significantly increases a history of SCC. The prevention and management of AK is a true challenge for patients, physicians, and health care policy makers.

Funding

This work was supported by The Netherlands Organization for Health Research and Development (ZonMw), project number 152001013/ VIDI 91711315.

INTRODUCTION

Actinic keratoses (AKs) are a common keratinocytic intra-epidermal neoplasia (KIN) often occurring on chronically sun-exposed skin of Caucasian individuals.[1] Although AKs may persist or spontaneously regress, AKs may progress to invasive cutaneous squamous cell carcinoma (SCC) in approximately 0.1 to 20% of the lesions annually.[2-4] Recently, a study suggested AKs may progress to basal cell carcinoma (BCC) as well.[5] AKs are often diagnosed clinically (i.e., rough red scaly patches on chronically sun-exposed skin) without histological confirmation and are, therefore, not recorded in pathology databases and cancer registries.

Population-based studies investigating AK prevalence and its associated risk factors[6-10] conclude that elderly subjects with European ancestry and high cumulative ultraviolet (UV) exposure have the highest risk of developing AKs. However these studies are few and report prevalences of AK varying from 1.4 to 59.2%. These differences in prevalences could be due to the geographic variability in UV radiation levels (Australia > United States of America > Europe) and the differences between the studied populations (e.g. high-risk patients, pigmentation status and age restrictions). Moreover skin examinations and AK count were not conducted uniformly in these studies.[6-11]

Most national guidelines or consensus reports recommend the treatment of AKs, for which a variety of modalities are available, and follow up of these patients because of their invasive potential. Implementing these recommendations puts a further burden on general physicians and the dermatological care that is already strained by the care of cutaneous malignancies.[12-13]

More accurate insight into the prevalence of AK among the general population is pivotal for public health strategies and medical decision makers. For the first time in The Netherlands, the prevalence of AK and its associated risk factors were investigated in a population-based cohort study (i.e. Rotterdam Study) among 2,061 elderly participants.

METHODS

Study population

The Rotterdam Study is an ongoing prospective population-based cohort study that follows inhabitants of the Ommoord district of Rotterdam, The Netherlands since 1990. The study design and objectives of the Rotterdam Study have been described elsewhere.[14] The Rotterdam Study was designed to study frequencies and risk factors associated with diseases of the elderly (e.g. coronary heart disease, Alzheimer disease and osteoporosis). Every 3 to 4 years, participants are interviewed at home and undergo an extensive set of examinations at the Rotterdam Study research facilities.

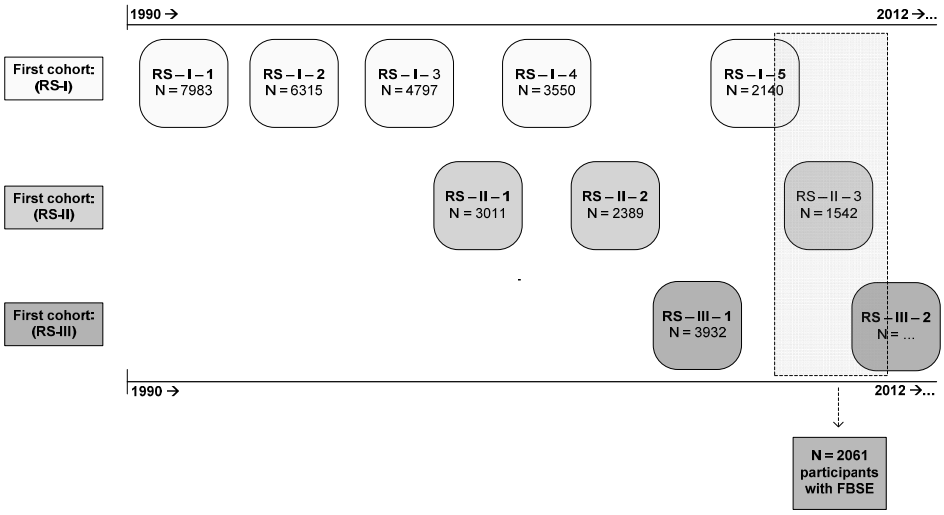

Figure 1. Flowchart of the Rotterdam Study
Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; RS, Rotterdam Study

In January 1990, the first cohort (RS-I) of 7,983 participants (78% of invitees) aged 55 years or older was established (Figure 1). In 2000, a second cohort (RS-II) was added to the Rotterdam Study, including 3,011 participants (67% of invitees) who had turned 55 years of age or had moved into the study district. The third cohort (RS-III) was established in 2006, in which 3,932 participants (65% of invitees) aged 45 to 54 years were added to the cohort. Participants of the present study were all above 50 years of age. The Rotterdam Study is approved by the Medical Ethics Committee of the Erasmus MC University Medical Center and The Netherlands Ministry of Health, Welfare and Sports.

Dermatology in the Rotterdam Study

In August 2010, dermatology was introduced to the Rotterdam Study (Figure 1). Since then, full body skin examinations (FBSE; with the exception of the feet and the skin covered by socks and underwear, respectively) are being conducted by four trained physicians focussing on the most common skin diseases such as skin (pre-)malignancies, atopic dermatitis, hand eczema, psoriasis and varicose veins.

Actinic keratoses

An AK was diagnosed clinically and was defined as a rough (keratotic) lesion with adherent scaling and erythema, not fitting another diagnosis.[15] Since AK lesions are often confluent and located on sun- damaged skin, it is difficult to count the total number of individual lesions within a participant.[15]

We counted overall number of AK per participant and subdivided this into the number of AK per localisation using the same categories: no presence of AK, 1 to 3, 4 to 9 or ≥ 10 AK. The subdivision per anatomical localisation consisted of the most important sun-exposed areas including scalp, face (excluding ears), ears, neck, back of hands, forearms, chest or other localisations.

Risk factors

Sex and age (in years) at date of skin examination were registered. Educational level (classified into 3 categories: low [primary education and primary education with a higher not completed education], medium [lower-level secondary education, lower-level vocational education intermediate-level vocational education], and high [general secondary education, higher-level vocational education and university]), smoking (never versus ever), hair color at young age (red, fair / blond, dark blond / brown and black) and four questions assessing UV exposure were available from interview data. The questions on UV exposure included tendency for sunburns, history of more than 25 years of outdoor work, having lived more than one year in a sunny country and sun-protective behavior (i.e. wearing sunglasses and/or a rimmed hat in the sunshine). The first three UV items had binary responses and the latter was categorized into never / almost never, often / not always and always. Eye color (blue, intermediate, brown) was available from and scored by the ophthalmology department within the Rotterdam study.

During FBSE, the following potential phenotypic risk factors for AK were scored; skin color (very white [3.4%], white [79.1%], white to olive [14.5%], light brown [1.7%], brown [1.1%], dark brown / black [0.2%]), Glogau score (type 1 'no wrinkles', type 2 'wrinkles in motion', type 3 'wrinkles at rest' and type 4 'only wrinkles')[16], number of naevi (< 25, 25 – 50, 50 – 100, > 100) and baldness of the scalp based on the Norwood – Hamilton (NH)[17-18] scale for men and the Ludwig scale (LS)[19] for women. In the analyses, baldness of the scalp was divided into none or minimal (NH score A,B,C,I,J and LS score 1), mild (NH score D,E,F,K and LS score 2) and extensive baldness (NH score G,H,L and LS score 3).

Due to significant correlation (phi-test for correlation, $p < 0.001$) between the phenotypic characteristics hair color at young age, eye - and skin color, these three variables were combined into one variable 'pigmentation status' and classified by light, medium or dark pigmentation status.

Skin cancer history

All RS participants were linked to PALGA, the Dutch nationwide network and registry of histo- and cytopathology in The Netherlands, which contains excerpts of all pathology reports with nationwide coverage from 1991 onwards.[20] A linkage between PALGA and our study population was made until September 23th 2011.[21] An excerpt encloses encrypted patient data, a summary of the pathology report and a diagnosis line based

upon standard pathology terminology similar to the Systematized Nomenclamenture of Medicine (SNOMED) issues by the College of American Pathologists. Individuals in the database have an encrypted patient identification code which enables linkage with all available pathology data within PALGA. The search in PALGA was based on codes corresponding to all types of BCC (i.e. M80903, M80913, M80923, M80933, M80943, M80963, M80973, M80983), SCC (i.e. M80703, M80713, M80723, M80743, M80753, M80704, M85603, M80711) and melanoma (i.e. M87203, M87213, M87223, M87233, M87263, M87303, M87403, M87423, M87433, M87443, M87453, M87700, M87703, M87713, M87723, M87743, M87753, M87803). Participants were counted only once per cutaneous malignancy (Figure 1).

Statistical analyses

The prevalence of AK within the 2,061 studied participants of the Rotterdam Study was standardized by age (5–year bands) and sex and 95% confidence intervals (95% CI) for proportion were calculated. The sex– and age-specific prevalences were multiplied by the sex- and age-specific population size in The Netherlands (5-year bands). Population size was obtained from Statistics Netherlands and estimated on the first of January 2011.[22] The extrapolated AK prevalence was calculated for the Dutch population aged 50 years or more.

To investigate risk factors associated with the development of AK, uni- and multivariate multinomial logistic regression analyses were performed and odds ratios (OR) with 95% CI were calculated for each of the three outcome groups, 1 to 3, 4 to 9 and ≥ 10 AK.

In addition, considering the ordinal structure of the latter outcome groups, an ordinal logistic regression was used to provide a cumulative OR. A significant cumulative OR corresponds to a statistically significant trend of increase in risk across the AK strata.[23-24] A corresponding p-value for trend (based on the ordinal logistic regression) was calculated (Table 4). However, not all variables met the proportional odds assumption for this test and fitted therefore better in the multinomial logistic regression model.

To compare participants with extensive actinic damage (≥ 10 AK) to those with no or less actinic damage (0 to 9 AK), uni- and multivariate binary logistic regression analyses were used to calculate (adjusted) OR with 95% CI. All variables included in the univariate analyses were included in the multivariate analyses as possible confounders for AK risk. No significant interaction terms were observed. All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS inc., Chicago, IL, USA). P-values were two–sided and considered statistically significant if p–value < 0.05.

RESULTS

In total, 2,061 (99.9%) of 2063 participants visiting the Rotterdam Study research facility between August 2010 and April 2012 agreed to undergo a FBSE. Hereof, 208 (10.1%) were from RS-I, 1,542 (74.8%) RS-II and 311 (15.1%) RS-III. The majority of the participants were women (55.0%; Table 1). Mean age at date of FBSE was 71.6 years (standard deviation [SD] 7.1; ranging from 51 to 98 years).

Table 1. Study characteristics of 2,061 participants of the Rotterdam Study with a full body skin examination

Characteristics	Total study population (n=2,061)	No AK (%) (n=1,288)	1 - 3 AKs (%) (n=433)	4 - 9 AKs (%) (n=177)	≥ 10 AKs (%) (n=163)
Sex					
Women	1,134 (55.0)	815 (63.3)	220 (50.8)	58 (32.8)	41 (25.2)
Men	927 (45.0)	473 (36.7)	213 (49.2)	119 (67.2)	122 (74.8)
Age at FBSE					
Mean age in years (SD)	71.6 (7.1)	70.2 (7.2)	73.0 (6.4)	74.1 (6.5)	75.6 (6.2)
< 70	874 (42.4)	638 (49.5)	156 (36.0)	50 (28.2)	30 (18.4)
70 - 79.99	947 (45.9)	532 (41.3)	219 (50.6)	98 (55.4)	98 (60.1)
≥ 80	240 (11.6)	118 (9.2)	58 (13.4)	29 (16.4)	35 (21.5)
Pigmentation status (based on eye, hair and skin color)					
Dark	212 (10.3)	164 (12.7)	26 (6.0)	12 (6.8)	10 (6.1)
Medium	1,294 (62.8)	813 (63.1)	272 (62.8)	116 (65.5)	93 (57.1)
Light	385 (18.7)	201 (15.6)	92 (21.2)	39 (22.0)	53 (32.5)
Data missing	170 (8.2)	110 (8.5)	43 (9.9)	10 (5.6)	7 (4.3)
Glogau scale					
1 and 2	180 (8.7)	156 (12.1)	17 (3.9)	5 (2.8)	2 (1.2)
3	1,684 (81.7)	1,026 (79.7)	359 (82.9)	154 (87.0)	145 (89.0)
4	197 (9.6)	106 (8.2)	57 (13.2)	18 (10.2)	16 (9.8)
Naevi					
< 25	1,569 (76.1)	985 (76.5)	323 (74.6)	130 (73.4)	131 (80.4)
25 – 50	385 (18.7)	236 (18.3)	90 (20.8)	35 (19.8)	24 (14.7)
50 or more	107 (5.2)	67 (5.2)	20 (4.6)	12 (6.8)	8 (4.9)
Baldness[1]					
No / almost no baldness	1,355 (65.7)	940 (73.0)	60 (13.9)	66 (37.3)	83 (50.9)
Mild baldness	389 (18.9)	240 (18.6)	86 (19.9)	35 (19.8)	28 (17.2)
Severe baldness	317 (15.4)	108 (8.4)	287 (66.3)	76 (42.9)	52 (31.9)
Tendency to develop sunburn					
Low	1,330 (64.5)	873 (67.8)	275 (63.5)	108 (61.0)	74 (45.4)
High	607 (29.5)	330 (25.6)	129 (29.8)	64 (36.2)	84 (51.5)
Data missing	124 (6.0)	85 (6.6)	29 (6.7)	5 (2.8)	5 (3.1)

Table 1 (continued)

Characteristics	Total study population (n=2,061)	No AK (%) (n=1,288)	1 - 3 AKs (%) (n=433)	4 - 9 AKs (%) (n=177)	≥ 10 AKs (%) (n=163)
Outdoor work history ≥ 25 years					
No	334 (16.2)	220 (17.1)	51 (11.8)	21 (11.9)	42 (25.8)
Yes	151 (7.3)	105 (8.2)	21 (4.8)	14 (7.9)	11 (6.7)
Data missing	1,576 (76.5)	963 (74.8)	361 (83.4)	142 (80.2)	110 (67.5)
History of living in sunny country of > 1 year					
No	1,730 (83.9)	1,064 (82.6)	367 (84.8)	163 (92.1)	136 (83.4)
Yes	213 (10.3)	145 (11.3)	37 (8.5)	9 (5.1)	22 (13.5)
Data missing	118 (5.7)	79 (6.1)	29 (6.7)	5 (2.8)	5 (3.1)
Sun protective behavior[2]					
Never / almost never	672 (32.6)	454 (35.2)	135 (31.2)	49 (27.7)	34 (20.9)
Often / not always	640 (31.1)	358 (27.8)	136 (31.4)	75 (42.4)	71 (43.6)
Always	631 (30.6)	397 (30.8)	133 (30.7)	48 (27.1)	53 (32.5)
Data missing	118 (5.7)	79 (6.1)	29 (6.7)	5 (2.8)	5 (3.1)
Smoking history					
Never	663 (32.2)	434 (33.7)	155 (35.8)	35 (19.8)	39 (23.9)
Ever	1,381 (67.0)	846 (65.7)	272 (62.8)	139 (78.5)	124 (76.1)
Data missing	17 (0.8)	8 (0.6)	6 (1.4)	3 (1.7)	0
Education level[3]					
Low	374 (18.1)	235 (18.2)	78 (18.0)	31 (17.5)	30 (18.4)
Medium	1,215 (59.0)	751 (58.3)	271 (62.6)	106 (59.9)	87 (53.4)
High	444 (21.5)	285 (22.1)	78 (18.0)	39 (22.0)	42 (25.8)
Data missing	28 (1.4)	17 (1.3)	6 (1.4)	1 (0.06)	4 (2.5)

Legend:

[1]Based on the Norwood – Hamilton scale for men and Luwdig scale for women.

[2]Wearing sunglasses and/or a rimmed hat in the sunshine.

[3]Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)

Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; SD, standard deviation; n, number

Prevalence of actinic keratoses

Of 2,061 participants, 773 (37.5%) had at least one or more AK of which 56.0% had 1 to 3 AK, followed by 4 to 9 (22.9%) and 10 or more (21.1%). Overall, the prevalence of one AK or more was 49.0% (95% CI 45.8–52.2%) for men and 28.1% (25.5–30.7%) for women (Table 2). AK prevalence increased with age in both men and women, but there was a small dip in age category 80 – 84 years compared to younger age–groups in men and women (Table 2 and Figure 2).

Table 2. Prevalence of actinic keratoses among 2061 participants of the Rotterdam Study

Age-groups in years	Total study population			Men			Women		
	Total n=2,061	AK (%) n=773	(95% CI)	Total n=927	AK (%) n=454	(95% CI)	Total n=1,134	AK (%) n=319	(95% CI)
50 - 54	49	0,0	(0.0 - 0.0)	16	0,0	(0.0 - 0.0)	33	0.0	(0.0 - 0.0)
55 - 59	74	6.8	(1.0 - 12.5)	31	12.9	(1.1 - 24.7)	43	2.3	(-2.2 - 6.8)
60 - 64	108	19.4	(12.0 - 26.9)	38	23.7	(10.2 - 37.2)	70	17.1	(8.3 - 25.9)
65 - 69	643	32.7	(29.0 - 36.3)	302	41.1	(35.6 - 46.6)	341	25.2	(20.6 - 29.8)
70 - 74	674	41.1	(37.4 - 44.8)	306	52.9	(47.3 - 58.5)	368	31.3	(26.6 - 36.0)
75 - 79	273	50.5	(44.6 - 56.6)	127	70.9	(63.0 - 78.8)	146	32.9	(25.3 - 40.5)
80 - 84	146	41.1	(33.1 - 49.1)	71	54.9	(43.3 - 66.5)	75	28.0	(17.8 - 38.2)
≥ 85	94	66.0	(56.4 - 75.6)	36	72.2	(57.6 - 86.8)	58	62.1	(49.6 - 74.6)
Overall	2,061	37.5	(35.4 - 39.6)	972	49.0	(45.8 - 52.2)	1,134	28,1	(25.5 - 30.7)

Abbreviations: AK, actinic keratoses, n, number

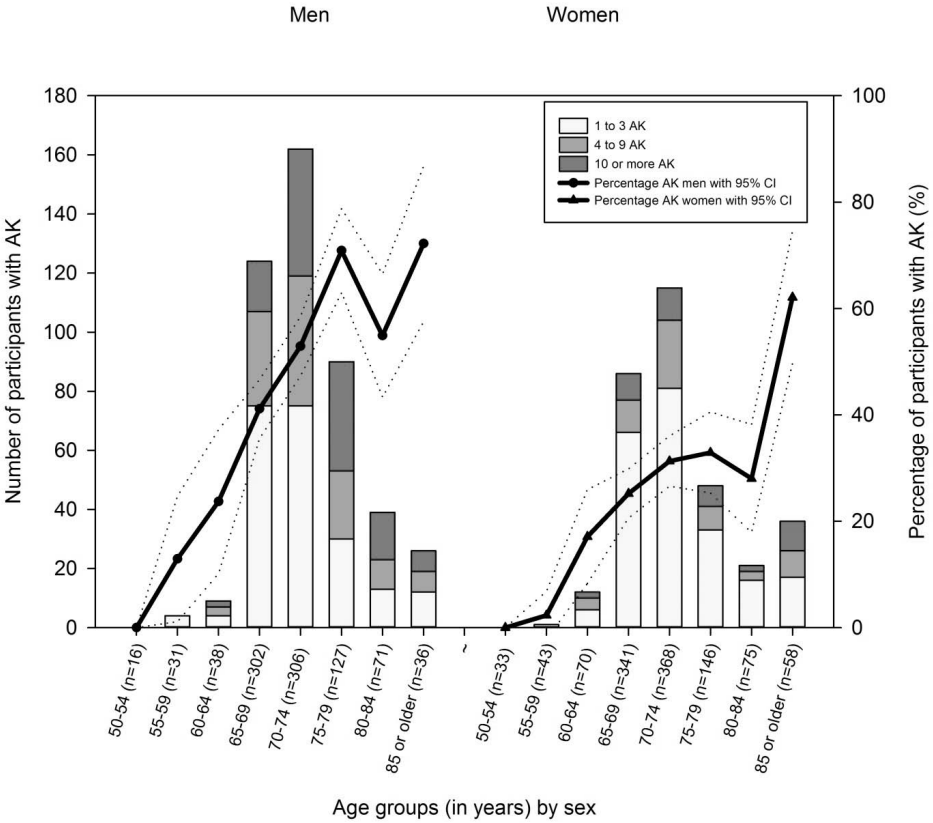

Figure 2. Prevalence of actinic keratoses among 2061 participants of the Rotterdam Study, stratified by sex
Abbreviations: AK, actinic keratoses; BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma

Extrapolation to The Netherlands showed that 1,408,641 of the 5,985,164 Dutch citizens aged fifty years or older were affected by AK in 2011, of which 817,823 (58%) were men and 596,487 (42%) were women. This corresponds to an AK prevalence of 23.5% (95% CI 21.7 – 25.3%) in the Dutch population aged 50 years or older; 28.8% (25.9–31.7%) for men and 19.0% (16.7–21.2%) for women.

Location of actinic keratoses

Overall, the face was the location most commonly affected by 1 to 3 (42.5%) and 4 to 9 (33.4%) AK, while ≥ 10 AK were more frequently located on scalp with 36.2% (Table 3). Stratification by sex showed that extensive actinic damage (≥ 10 AK) was most often found on scalp (47.5%) in bald men, while this was 0.0% in women. In women, extensive actinic damage was most often located on the face followed by chest, respectively 32.2% and 29.0% (Table 3).

Table 3. Anatomical location of actinic keratoses among 774 participants of the Rotterdam Study with actinic keratoses

	Study population			Men			Women		
Number of AK	**1 to 3 n = 891**	**4 to 9 n = 290**	**≥ 10 n = 130**	**1 to 3 n = 506**	**4 to 9 n = 205**	**≥ 10 n = 99**	**1 to 3 n = 385**	**4 to 9 n = 85**	**≥ 10 n = 31**
Localisation									
Scalp	117 (13.1)	84 (29.0)	47 (36.2)	109 (21.5)	82 (40.0)	47 (47.5)	8 (2.1)	2 (2.4)	0 (0.0)
Face	379 (42.5)	97 (33.4)	35 (26.9)	182 (36.0)	64 (31.2)	25 (25.3)	197 (51.2)	33 (38.8)	10 (32.3)
Ears	83 (9.3)	11 (3.8)	0 (0.0)	71 (14.0)	10 (4.9)	0 (0.0)	12 (3.1)	1 (1.2)	0 (0.0)
Neck	8 (0.9)	2 (0.7)	1 (0.8)	6 (1.2)	1 (0.5)	0 (0.0)	2 (0.5)	1 (1.2)	1 (3.2)
Back of hands	116 (13.0)	37 (12.8)	9 (6.9)	63 (12.5)	24 (11.7)	6 (6.1)	53 (13.8)	13 (15.3)	3 (9.7)
Forearms	76 (8.5)	30 (10.3)	12 (9.2)	34 (6.7)	12 (5.9)	7 (7.1)	42 (10.9)	18 (21.2)	5 (16.1)
Chest	72 (8.1)	18 (6.2)	14 (10.8)	26 (5.1)	4 (2.0)	5 (5.0)	46 (11.9)	14 (16.5)	9 (29.0)
Elsewhere	40 (4.5)	11 (3.8)	12 (9.2)	15 (3.0)	8 (3.9)	9 (9.1)	25 (6.5)	3 (3.5)	3 (9.7)

Abbreviations: AK, actinic keratoses; n, number

Risk factors of actinic keratoses

Male sex, age of 70 years and older, medium and dark pigmentation status, Glogau score 3 and 4, high tendency for sunburn and often / not always use of sun protective measurements were all significantly associated with the three outcome groups in the univariate multinomial logistic regression analysis (Appendix Table 1). Medium baldness was associated with 4 to 9 (OR 1.8 [95% CI 1.2 – 2.8]) and ≥ 10 AK (OR 2.1 [95% CI 1.3 – 3.4]), whereas severe baldness was associated with all three outcome groups in a linear manner up to an OR 13.9 (9.3 – 20.7) for >10 AKs compared to no or minimal hairloss. Naevi and educational level were not significantly associated with

AK, whereas ever smoking was associated with 4 to 9 and ≥ 10 AK (OR 2.0 [95% CI 1.4 – 3.0] and OR 1.6 [95% CI 1.1 – 2.4], respectively). All variables remained significantly associated with AKs in the multivariate multinomial model (Table 4). After adjusting for the other risk factors, severe baldness remained the strongest risk factor for ≥ 10 AK (adjusted OR 6.3 [95% CI 3.6– 1.0]; p-value for trend < 0.001). After stratification by sex (data not shown), severe baldness remained significantly associated with ≥10 AK in men (adjusted OR 7.0 [3.8–13.1]), but not in women (no OR could be calculated since only 8 women had severe baldness). Male sex, age of 70 years or older, Glogau 3 and 4 and tendency to develop sunburn remained significantly associated with all three outcome groups. Light pigmentation status was associated with 1 to 3 (OR 2.3 [95% CI 1.3 – 3.8]) and ≥ 10 AK (OR 2.5 [95% CI 1.1 – 5.7]), but not with 4 to 9 AK. Always use of sun protective measurement was associated with ≥ 10 AK (adjusted OR 2.0 [95% CI 1.2 – 3.4]).

Table 4. Multivariate multinomial logistic regression: risk factors associated with actinic keratoses among 2,061 participants of the Rotterdam Study

Characteristics	1 - 3 AKs adjusted odds ratio (95% CI)	4 - 9 AKs adjusted odds ratio (95% CI)	≥ 10 AKs adjusted odds ratio (95% CI)	P – value[4] (based on ordinal logistic regression)
Sex				
Women	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Men	**2.2 (1.6 -2.9)**	**2.5 (1.5 - 3.9)**	**3.2 (1.8 - 5.6)**	p < 0.001
Age at clinical examination				
< 70	1.0 (ref)	1.0 (ref)	1.0 (ref)	
70 - 79.99	**1.6 (1.2 - 2.1)**	**2.0 (1.4 - 3.0)**	**3.7 (2.3 - 6.0)**	p < 0.001
≥ 80	**1.7 (1.1 - 2.7)**	**2.7 (1.5 - 5.0)**	**6.5 (3.4 - 12.4)**	p < 0.001
Pigmentation status (based on eye, hair and skin color)				
Dark	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Medium	**1.7 (1.1 - 2.8)**	1.5 (0.8 - 3.0)	1.3 (0.6 - 2.7)	p = 0.05
Light	**2.3 (1.3 - 3.8)**	1.9 (0.9 - 4.1)	**2.5 (1.1 - 5.7)**	p < 0.001
Glogau				
1 and 2	1.0 (ref)	1.0 (ref)	1.0 (ref)	
3	**3.7 (1.9 - 7.0)**	**4.1 (1.4 - 11.7)**	**8.0 (1.9 - 34.8)**	p < 0.001
4	**5.5 (2.6 - 11.5)**	**4.9 (1.5 - 16.2)**	**6.0 (1.2 - 29.4)**	p < 0.001
Naevi				
< 25	1.0 (ref)	1.0 (ref)	1.0 (ref)	
25 – 50	**1.4 (1.0 - 1.9)**	1.3 (0.8 - 2.0)	1.0 (0.6 - 1.8)	p = 0.15
50 or more	1.3 (0.7 - 2.2)	1.6 (0.8 - 3.4)	1.3 (0.5 - 3.2)	p = 0.29

Table 4 (continued)

Characteristics	1 - 3 AKs adjusted odds ratio (95% CI)	4 - 9 AKs adjusted odds ratio (95% CI)	≥ 10 AKs adjusted odds ratio (95% CI)	P – value[4] (based on ordinal logistic regression)
Baldness[1]				
No / almost no baldness	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Mild baldness	0.8 (0.6 - 1.1)	1.1 (0.7 - 1.8)	1.2 (0.7 - 2.0)	p = 0.79
Severe baldness	**1.2 (0.8 - 1.8)**	**4.1 (2.5 - 6.8)**	**6.3 (3.6 - 11.0)**	p < 0.001
Tendency to develop sunburn				
Low	1.0 (ref)	1.0 (ref)	1.0 (ref)	
High	**1.4 (1.0 - 1.8)**	**2.0 (1.3 - 2.9)**	**3.3 (2.2 - 5.0)**	p < 0.001
Data missing				
Outdoor work history ≥ 25 years				
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Yes	0.9 (0.5 - 1.7)	1.6 (0.7 - 3.5)	0.6 (0.3 - 1.5)	p = 0.60
Data missing	1.0 (ref)	1.0 (ref)	1.0 (ref)	
History of living in sunny country of > 1 year				
No	0.8 (0.5 - 1.2)	**0.3 (0.1 - 0.7)**	0.7 (0.4 - 1.3)	p = 0.01
Yes	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Data missing	1.3 (0.9 - 1.7)	**1.9 (1.3 - 2.0)**	**2.5 (1.5 - 4.1)**	p < 0.001
Sun protective behavior[2]				
Never / almost never	1.2 (0.9 - 1.6)	1.2 (0.8 - 2.0)	**2.0 (1.2 - 3.4)**	p = 0.02
Often / not always	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Always	**0.7 (0.5 - 0.9)**	1.3 (0.8 - 2.0)	0.9 (0.6 - 1.4)	p = 0.4
Data missing				
Smoking history	1.0 (ref)	1.0 (ref)	1.0 (ref)	
Never	1.1 (0.8 - 1.4)	1.1 (0.7 - 1.8)	0.9 (0.5 - 1.4)	p = 0.84
Ever	0.8 (0.5 - 1.1)	1.0 (0.6 - 1.7)	0.9 (0.5 - 1.6)	p = 0.27

Legend:

[1] Based on the Norwood – Hamilton scale for men and Luwdig scale for women

[2] Wearing sunglasses and/or a rimmed hat in the sunshine

[3] Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)

[4] P-value based on multivariate ordinal logistic regression

Abbreviations: AK, actinic keratoses; FBSE, full body skin examination; ref, reference group

In line with the multinominal model, the multivariate binary logistic regression showed that men, older age (≥ 70 years), Glogau score 3, medium and severe baldness, high tendency to develop sunburn, and often /not always and always use of sun protective measurements were significantly associated with extensive actinic damage (>10 AKs) (Table 5).

Table 5. Risk factors associated with extensive actinic damage (≥ 10 actinic keratoses) among 2061 participants of the Rotterdam Study

Characteristics	0 - 9 AK n =1,898	≥ 10 AK n = 163	≥ 10 AK crude odds ratio (95% CI)	≥ 10 AK adjusted odds ratio (95% CI)
Sex				
Women	1,093 (42.4)	41 (25.2)	1.0 (ref)	1.0 (ref)
Men	805 (42.4)	122 (74.8)	**4.0 (2.8 – 5.8)**	**2.3 (1.4 - 4.0)**
Age at clinical examination				
< 70	844 (44.5)	30 (18.4)	1.0 (ref)	1.0 (ref)
70 - 79.99	849 (44.7)	98 (60.1)	**3.2 (2.1 – 4.9)**	**2.9 (1.8 - 4.6)**
≥ 80	205 (10.8)	35 (21.5)	**4.8 (2.9 – 8.0)**	**4.7 (2.5 - 8.7)**
Pigmentation status (based on eye, hair and skin color)				
Dark	202 (10.6)	10 (6.1)	1.0 (ref)	1.0 (ref)
Medium	1,201 (63.3)	93 (57.1)	1.6 (0.8 – 3.1)	1.0 (0.5 - 2.2)
Light	332 (17.5)	53 (32.5)	**3.2 (1.6 – 6.5)**	1.8 (0.8 - 4.1)
Data missing	163 (8.6)	7 (4.3)		
Glogau				
1 and 2	178 (9.4)	2 (1.2)	1.0 (ref)	1.0 (ref)
3	1,539 (81.1)	145 (89.0)	**8.4 (2.1 - 34.1)**	**5.4 (1.3 - 22.9)**
4	181 (9.5)	16 (9.8)	**7.9 (1.8 - 34.7)**	3.4 (0.7 - 16.4)
Naevi				
< 25	1,438 (75.8)	131 (80.4)	1.0 (ref)	1.0 (ref)
25 - 50	361 (19.0)	24 (14.7)	0.7 (0.5 – 1.1)	1.1 (0.5 - 2.5)
> 50	99 (5.2)	8 (4.9)	0.9 (0.4 – 1.9)	0.9 (0.5 - 1.5)
Baldness[1]				
No / almost no baldness	1,303 (68.7)	83 (50.9)	1.0 (ref)	1.0 (ref)
Mild baldness	361 (19.0)	28 (17.2)	**1.9 (1.2 – 3.1)**	**1.2 (0.7 - 2.1)**
Severe baldness	234 (12.3)	52 (31.9)	**8.9 (6.1 - 12.9)**	**4.5 (2.6 - 7.5)**
Tendency to develop sunburn				
Low	1,256 (66.2)	74 (45.4)	1.0 (ref)	1.0 (ref)
High	523 (27.6)	84 (51.5)	**2.7 (2.0 – 3.8)**	**2.7 (1.8 - 4.0)**
Data missing	119 (6.3)	5 (3.1)		

Table 5 (continued)

Characteristics	0 - 9 AK n =1,898	≥ 10 AK n = 163	≥ 10 AK crude odds ratio (95% CI)	≥ 10 AK adjusted odds ratio (95% CI)
Outdoor work history ≥ 25 years				
No	292 (15.4)	11 (6.7)	1.0 (ref)	1.0 (ref)
Yes	140 (7.4)	42 (25.8)	0.5 (0.3 – 1.1)	0.6 (0.3 - 1.3)
Data missing	1,466 (77.2)	110 (67.5)		
History of living in sunny country of > 1 year				
No	1,594 (84.0)	136 (83.4)	1.0 (ref)	1.0 (ref)
Yes	191 (10.1)	22 (13.5)	1.4 (0.8 – 2.2)	0.9 (0.5 - 1.6)
Data missing	113 (6.0)	5 (3.1)		
Sun protective behavior[2]				
Never / almost never	638 (33.6)	34 (20.9)	1.0 (ref)	1.0 (ref)
Often / not always	569 (30.0)	71 (43.6)	**2.3 (1.5 – 3.6)**	**2.1 (1.3 - 3.3)**
Always	578 (30.5)	53 (32.5)	**1.7 (1.1 – 2.7)**	**1.9 (1.1 - 3.1)**
Data missing	113 (6.0)	5 (3.1)		
Smoking history				
Never	624 (32.9)	39 (23.9)	1.0 (ref)	1.0 (ref)
Ever	1,257 (66.2)	124 (76.1)	**1.6 (1.1 – 2.3)**	0.9 (0.6 - 1.4)
Data missing	17 (0.9)	0 (0.0)		
Education level[3]				
Low	402 (21.2)	30 (18.4)	1.0 (ref)	1.0 (ref)
Medium	1,128 (59.4)	87 (53.4)	0.9 (0.6 – 1.4)	0.9 (0.5 - 1.7)
High	402 (21.2)	42 (25.8)	1.2 (0.7 – 2.0)	1.8 (0.4 - 8.5)
Data missing	24 (1.3)	4 (2.5)		

Legend:

[1] Based on the Norwood – Hamilton scale for men and Luwdig scale for women

[2] Wearing sunglasses and/or a rimmed hat in the sunshine

[3] Low (primary education and primary education with a higher not completed education), medium (lower-level secondary education, lower-level vocational education intermediate-level vocational education), and high (general secondary education, higher-level vocational education and university)

Abbreviations: AK, actinic keratoses; FBSE, full body skin examination

Skin cancer history and detection during FBSE

In total, 238 (11.5%) participants had a history of BCC, 51 (2.5%) of SCC and 20 (0.5%) of melanoma. The risk of a history with one of these cutaneous malignancies increased across the AK severity strata (i.e. from none to >10 AKs). For BCC, SCC and melanoma, these risks increased respectively from 7.2 to 26.5%, 1.2 to 13.6% and 0.7 to 1.9% (Figure 3). Although these risks increased gradually for BCC and melanoma, a sharper increase was seen for SCC. Participants with >10 AKs (13.6%) had a three fold higher risk for having

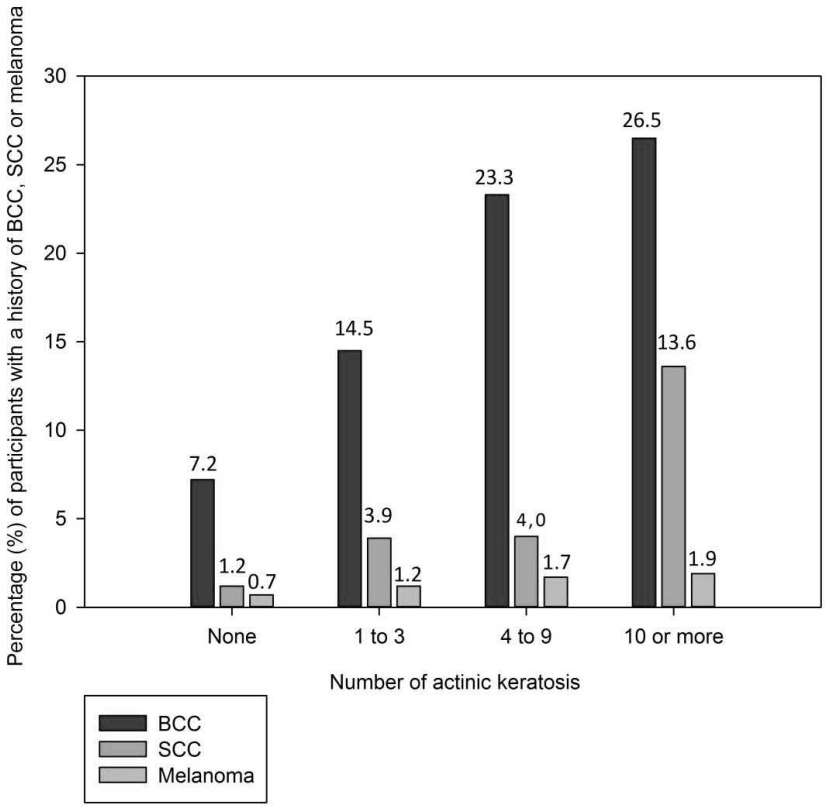

Figure 3. Percentage of participants with and withouth actinic keratoses who have a history of squamous cell carcinoma (SCC), basal cell carcinoma (BCC) or melanoma
Abbreviations: AK, actinic keratoses; BCC, basal cell carcinoma; SCC, squamous cell carcinoma

a SCC history compared to participants with 4 to 9 AKs (4.0%). Of the 2061 participants who received a FBSE during our study period, it was histologically confirmed that 59 (2.9%) had a BCC, 11 (0.5%) had a SCC and 9 (0.4%) a melanoma (including 5 invasive and 4 in situ). Overall, the detection rate of these cutaneous malignancies in our study population was 4.0% (82 out of 2,061 participants).

DISCUSSION

In this Dutch population-based study among more than 2,000 people with a mean age of 72 years who were examined by trained physicians, almost 38% had one or more AK and 8% had 10 or more (age- and sex-adjusted 23% and 5%, respectively). This AK prevalence is the highest overall AK prevalence in people aged 50 years or older when

compared to previous European population-based studies and comparable or less to studies from the United States of America (USA) and Australia.[7,9]

In Europe, the South Wales Skin Cancer Study observed an AK prevalence of 23% (95% CI 19.5 – 26.5), unadjusted for age and sex, among 1,034 persons aged 60 years or more. The lower prevalence may be explained by the fact that skin examinations were limited to the head and neck, lower arms (until shoulders), lower legs and feet and performed by research registrars in dermatology. Recently, in the PRAKTIS study a representative sample of 12,483 people of the Italian population aged > 45 years were selected by a stratified random sampling design in which 1.4% was affected by AK.[7] Again, skin examinations were performed by 'interviewers' and limited to the face and upper extremities.[7] In addition, the distribution of phenotypic characteristics of the Dutch (i.e. light skin, hair and eyes) increase the risk for AK development when compared to the the distribution in the Italian population with slightly darker skin, hair and eyes. German studies using claims data estimated an AK prevalences ranging from 2 to 31%, but these data were not population-based and included dermatology patients[25-26], patients without history of skin cancer who were invited to undergo skin examination when visiting their practice-based physician[16] or healthy workers who could undergo a voluntary FBSE at their work.[27] Between 1971-1975, a population-based study across the USA[8], in which 101 dermatologists performed FBSE in more than 8,000 white participants aged between 25 and 74 years, observed a crude AK prevalence of around 17%.[8] More recently, the crude prevalence for AK in the USA was estimated to be 45% in men aged 65 years or older and 35% in women.[28] Two Australian studies from the eighties who screened 2,095 and 1,040 people randomly selected from sample state electoral roll demonstrated that 40-60% of the participants had at least one AK.[6,10]

Risk factors and implications

Multiple risk factors were found to be associated with AK development confirming findings of previous studies assessing AK and SCC risk factors.[29-30] In men, baldness was found to be the strongest risk factor for presence of AK and severe actinic skin damage, probably because it continuously exposes the scalp in a horizontal plane to UV radiation resulting in high cumulative UV doses. In clinical practice, these patients with large cutaneous fields affected by AKs on the scalp are numerous and difficult to manage.

Patients possessing risk factors associated with extensive actinic damage such as severe baldness may require directed public health campaigns, a case-finding approach (i.e., inspection of the bald scalp during physician visits) including providing more information on sun protection and behavior.

In the past decade, pharmaceutical companies have focused on AK treatments resulting in new treatments other than cryotherapy, namely fluorouracil, imiquimod, photodynamic therapy and most recently Ingenol mebutate gel.[31-32] Recently, topical tretinoin

failed to act as a chemopreventive agent for AK development[33], whereas sunscreen use is effective in both AK and SCC prevention.[34-35]

Although it remains controversial whether or not to actively treat AKs (as not all will progress to SCC), people with multiple lesions (in this study defined as ≥10) are most likely to benefit from treatment and require a closer follow-up over time to prevent or detect the early development of SCC. Even this conservative approach is a health care challenge because it involves 5% of the Dutch 50-plus citizens (approximately 300,000 people) and this proportion is likely to increase over time. This is confirmed by a quick review of the claims data demonstrating that dermatologist reported twice as many AK related visits and treatment between 2007 and 2011 (from 42,115 to 76,395) emphasizing the strain cutaneous (pre-)malignancies put on the health care system.[36]

Strengths and limitations

The fact that FBSE were performed by a few trained physicians in more than 2,000 participants from a population-based study makes the Dutch point prevalence highly accurate. In general, AK have a typical presentation and are therefore clinically diagnosed by dermatologists and general practitioners. However AK can resemble keratinocyte carcinoma (including BCC and SCC), possibly leading to misclassification and an under or overestimation of AK in this study.[5] Nevertheless, this possible non – differential misclassification is considered small as trained physicians performed FBSE and previous studies observed a positive predictive value for AK diagnosis ranging from 74 to 94%.[37-38] In this study, AK prevalence was determined cross-sectionally and it was unknown whether participants were previously treated for AK which also could have resulted in an underestimation of the Dutch AK prevalence. Unfortunately, the design of the study does not allow a longitudinal follow up of individual AK to study its natural course. The individual number of AK lesions within a participant was not counted; instead AK presence was divided into three categories (i.e., 1 to 3, 4 to 9, ≥ 10). Although categorical data is less precise than continuous, previous studies showed that the inter-observer variation between dermatologists was large when counting the individual number of AK lesions within a participant and using categorised data greatly reduced this variation.[15] The population of the Rotterdam Study is 45 years and older and almost exclusive Caucasian possibly limiting the generalizibility of the findings. However, none of the participants aged below 55 years (n = 50) had AK and AKs are rare in people with darker skin suggesting that the extent of this limitation is rather small. At time of FBSE, only feet and areas covered by underwear were not examined because of practical and psychological reasons. It is unlikely that this restriction resulted in an underestimation of the AK prevalence because these areas are not chronically UV exposed.

CONCLUSIONS

More than a quarter of people are affected by AK and 8% by 10 or more lesions emphasizing that cutaneous (pre)maligancies are an enormous burden for health care providers. Preventive measures including promoting sun protective behavior, and raising awareness on cutaneous keratinocyte carcinoma and persistent AKs, should focus in particular on elderly, bald men and those with photodamaged facial skin to reduce the number of SCC.

ACKNOWLEDGEMENTS

The authors thank the participants of the Rotterdam Study for their participation and the research physicians and assistants for the data collection. We would like to thank Loes Hollestein for the statistical assistance and Robert Stern for critically reviewing the manuscript.

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Part III

Survival

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CHAPTER 9

Conditional survival of malignant melanoma in the Netherlands: 1994-2008

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Eur J Cancer. 2014 Feb;50(3):602-10.

ABSTRACT

Background

Cutaneous malignant melanoma causes the majority of skin cancer related deaths and features increasing incidence and mortality rates in the Netherlands. Conditional survival analysis is performed on patients who survived the preceding year(s).

Methods

Patients with invasive melanoma, as recorded in the population-based Netherlands Cancer Registry, were included. To assess prognosis of melanoma survivors according to gender and Breslow thickness, conditional five-year relative survival was calculated for lymph node negative melanoma patients and conditional one-year relative survival was analysed for melanoma patients with and without nodal involvement.

Findings

Between 1994 and 2008, 40,050 patients developed a melanoma (stage I-III, of whom 6% with nodal involvement). Six to eight years after diagnosis, survival of patients with a 1-2 mm (T2) thick melanoma equalized the general population. Conditional five-year relative survival for patients with >4mm thick (T4) melanomas increased from about 60% at diagnosis to 90% at 7 years after diagnosis. Largest improvements were found in patients with thick melanomas and female patients with nodal involvement.

Interpretation

The prognosis for melanoma survivors improved with each additional year of survival after diagnosis, except for patients with a ≤1mm thick melanoma, who never had any excess mortality during follow-up. Conditional survival of melanoma was better among females, among those with lower Breslow thickness, and nodal stage.

Funding

This work was supported by the Dutch Cancer Society [Grant number IKZ 2009-4316], project 'Insight into health aspects of long-term cancer survivors in the Netherlands – a tool for caregivers and cancer survivors').

INTRODUCTION

Cutaneous malignant melanoma encompasses a large variety of malignancies with different disease presentations and short-term outcomes. Cutaneous malignant melanoma causes the majority of skin cancer related deaths and is currently the sixth most common cancer in the Netherlands (excluding keratinocyte carcinomas of the skin) with continuously increasing incidence rates of 4% annually.[1] Similar rising trends have been reported in most European countries, while Australia, New Zealand, North America, and Israel showed a stabilizing or declining trend (mainly youngest age groups).[2] Norway has decreasing incidence trends in young age groups and increasing trends in older patients.[3] Mortality rates increased in the Netherlands[1] and several other European countries,[4] but remained stable or decreased in Scotland, the United Kingdom, Denmark (females), Iceland (males) the United States, and Australia.[5-11]

Survival estimates for cancer patients are traditionally reported from the time since cancer diagnosis and do not provide estimates for patients who have already survived a period of time after initial diagnosis and treatment. Patients diagnosed with nodal or distant metastases often die soon after diagnosis and negatively affect standard survival curves which are estimated at time of diagnosis. The right side of melanoma Kaplan-Meier survival curves show that there is generally a proportion of patients that have a better survival. The increasing incidence and relatively good survival, mostly due to thin melanomas, have resulted in a growing group of melanoma survivors. At the same time, patients with early nodal metastases (i.e. Sentinel Node (SN) positive patients), who have survived for 2-3 years after initial surgery, have a large chance to survive for a longer period of time. Conditional survival analysis is a method to estimate the survival rate of patients who already survived a certain period of time, i.e. patients on the right side of Kaplan-Meier survival curves.

These estimates give important information to cancer patients, i.e. almost a third of cancer survivors in the Netherlands experienced either changes in their work situation, problems with life insurances and/or problems regarding house mortgages due to their cancer.[12] These problems could decrease several years after diagnosis if conditional survival show trends to 100%.

Recent studies reported conditional survival estimates for melanoma in Europe[10,13-15], Australia[16], and the USA.[17-20] In this study, we present conditional 5-year relative survival rates for Dutch melanoma patients without nodal involvement and conditional 1-year relative survival rates for patients with and without nodal involvement, stratified for gender and Breslow thickness. This stratification is useful for caregivers and patients to be informed on their prognosis years after their initial diagnosis.

METHODS

Data collection

For this study, population-based data was used from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres.[1] The NCR is primarily based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathology archive (PALGA).[1] Information on patient characteristics such as gender and date of birth, as well as tumour characteristics such as date of diagnosis, location (International Classification of Diseases for Oncology (ICD-O-3)[21]), histology, Breslow thickness, stage, and grade, are routinely obtained from the medical records.[1] The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness of the NCR is estimated to be at least 95%.[22]

For the present study, all cases with stage I-III histologically proven invasive melanoma (C44) without distant metastasis (M0) diagnosed in the period 1994-2008 in the Netherlands were included (n=40,050). This study focussed on stage I-III patients, since stage IV patients generally have a poor survival and the number of patients in this group is too low to calculate accurate conditional survival estimates. Follow-up of vital status was complete until January 2010. Patients younger than 15 years and older than 89 years at diagnosis were excluded from the analysis, as well as cases diagnosed by autopsy. Age was divided in three groups (15-44, 45-59, 60-89 years). Breslow thickness was divided into four groups (≤1.0 mm, 1.01-2.0, 2.01-4.0, and >4.0 mm) according to the 7th edition (2009) of the American Joint Committee on Cancer (AJCC) staging system (T1,T2,T3, and T4; www.cancerstaging.org). Nodal involvement was grouped in node-positive (N+, consisting of N1, N2 or N3) and node-negative (N0, consisting of N0 or unknown nodal stage). Full stage according to AJCC could not be used, because criteria changed during the study period and subgroups became too small. Melanoma localization was categorized into head and neck (C44.0-C44.4), trunk (C44.5, C44.9), and extremities (arms and legs, C44.6, C44.7). Morphology was categorized into nodular melanoma (ICD-O3 8721), superficial spreading melanoma (ICD-O3 8742), and other melanoma subtypes (ICD-O3 8720-8780 excluding 8721 and 8742).

Statistical analyses

Conditional relative survival rates are relative survival rates for every additional year survived up to several years after diagnosis, conditional on being alive at the beginning of that year. Thus conditional five-year relative survival is the relative survival of patients alive five years after initial diagnosis.

Relative survival is the survival taking into account the background mortality of a population. It is calculated as the absolute survival among cancer patients divided

by the expected survival of a comparable group from the general population (same period, age, and gender). Expected survival was calculated from population life tables, according to Ederer II.[23] To provide up-to-date survival estimates, period analysis[24-26] was used. All observations included in the analysis are truncated (limited) at the beginning of the period of interest (e.g. one or five year(s) before the year of estimation) as well as censored at the end of follow-up.

Furthermore, to enable the estimation of even more up-to-date survival, hybrid analysis was used,[27] since follow-up of the study population (mortality data) is available up to 2009, while incidence data are only available up to 2008. This means that for the estimation of 5-year relative survival for patients diagnosed in 2008 we included the follow-up of years 2004–2008 (Supplemental Figure 1).

Five-year relative survival rates were computed for every additional year survived up to 11 years after diagnosis, conditional on being alive at the beginning of that year (conditional 5-year relative survival, 5-year CRS). Five-year CRS was computed according to Breslow thickness and gender. One-year CRS was analyzed for melanoma patients according to nodal status up to 15 years after diagnosis to estimate the short-term prognosis for melanoma patients taking into account the time a patient has already survived. Estimates for N+ patients could only be presented for limited time after diagnosis up to maximal 10 years due to relatively small groups of patients. It was not possible to calculate 5-year CRS for all N+ melanoma patients due to the small number of patients in the subgroups, stratified by Breslow thickness and gender, combined with the poor prognosis of many patients in this group. One-year and 5-year CRS analyses were also stratified for age groups, histological subtype, and tumour location to examine differences in survival. We presented only CRS estimates based on sufficiently large groups of patients. Therefore, CRS estimates were limited to results with a standard error ≤5% of the survival rate to avoid results based on chance. Minimal excess mortality was defined as a 5-year CRS which persistently reached 95% for a group of patients. Calculations were performed with SAS software (SAS system 9.2, SAS Institute, Cary, NC). This study was reported according to the STROBE criteria for cohort studies(http://www.strobe-statement.org).

RESULTS

A total of 40,050 patients (16,942 men and 23,108 women) were diagnosed with a stage I-III melanoma (N+ :6%, N0: 94%) between 1994 and 2010. The median ages of male and female patients were 56 (interquartile range (IQR): 44-67) and 52 (IQR: 40-65). The median (IQR) follow-up time was 5.4 (IQR: 2.8-9.4) years (males: 4.8 [2.5-8.6] years, females: 5.8 [3.0-9.8] years). Female patients had more thin melanomas (T1, Breslow thickness ≤1.0 mm) compared to male patients (54% vs. 44%, p<0.0001). Thick

Table 1. Characteristics of patients with stage I-III melanoma in the Netherlands, 1994-2008 (*n*=40,050)

	Men (*n*=16,942)		Women (*n*=23,108)		Total	
	n	**%**	***n***	**%**	***n***	**%**
Age (yrs)						
15-44	4,337	25	8,052	35	12,389	31
45-59	5,553	33	7,106	31	12,659	32
60-89	7,052	42	7,950	34	15,002	37
Breslow thickness (mm)						
≤1.0 (T1)	7,534	44	12,534	54	20,068	50
1.01-2.0 (T2)	3,766	22	4,965	22	8,731	22
2.01-4.0 (T3)	2,798	17	2,707	12	5,505	14
>4.0 (T4)	1,804	11	1,412	6	3,216	8
Missing/unknown	1,040	6	1,490	6	2,530	6
N stage						
N0	15,534	92	22,013	95	37,547	94
N+	1,408	8	1,095	5	2,503	6
Morphology						
Nodular melanoma	2,821	17	2,843	12	5,664	14
Superficial melanoma	9,968	59	14,658	64	24,626	61
Other	4,153	24	5,607	24	9,760	24
Location						
Head and neck	2,793	16	2,449	11	5,242	13
Trunk	8,325	49	6,340	27	14,665	37
Extremities	5,817	34	14,313	62	20,130	50
Unknown	7	0	6	0	13	0

Abbreviations: N0, no nodal involvement; N+, nodal involvement; *n*, number. Source: Netherlands Cancer Registry.

melanomas (T4, >4.0 mm) were diagnosed in 11% of the male patients and 6% of the female patients (Table 1).

Conditional 5-year relative survival in N0 patients

Five-year CRS remained almost 100% for both males and females with a melanoma of ≤1.0 mm (T1), indicating that these patients experience the same survival as the general Dutch population with the same age and gender as the patients. (Figure 1a and 1b) Five-year relative survival at diagnosis for male patients with a melanoma with a higher Breslow thickness were significantly lower with a 5-year relative survival ranging from 58% for >4.0 mm(T4) to 88% for 1.01-2.0 mm. For female patients this was higher with the 5-year relative survival ranging from 63% for >4.0 mm (T4) to 95% for 1.01-2.0 mm (T2). However, 5-year CRS for these Breslow categories quickly improved with time since

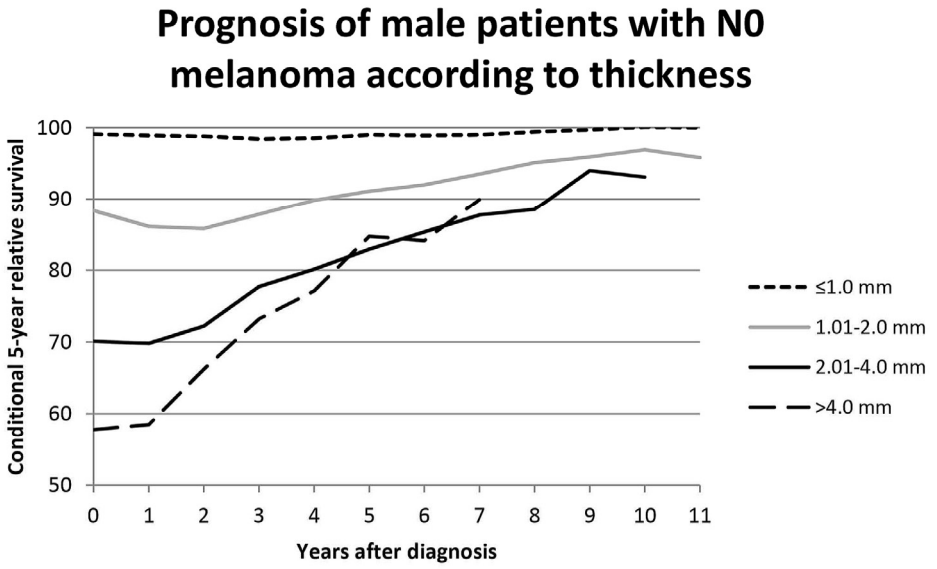

Figure 1a: 5-year relative survival at each time point after diagnosis for lymph node negative male patients who have already survived the previous year(s). E.g. male patients with Breslow thickness 2.01-4.0 mm at diagnosis who have already survived for 4 years, had a 80% chance to survive another 5 years (this means up to 9 years after diagnosis). When 5-year relative survival approached 100%, melanoma patients then alive had a prognosis similar to the background population (no excess mortality anymore). Source: Netherlands Cancer Registry.

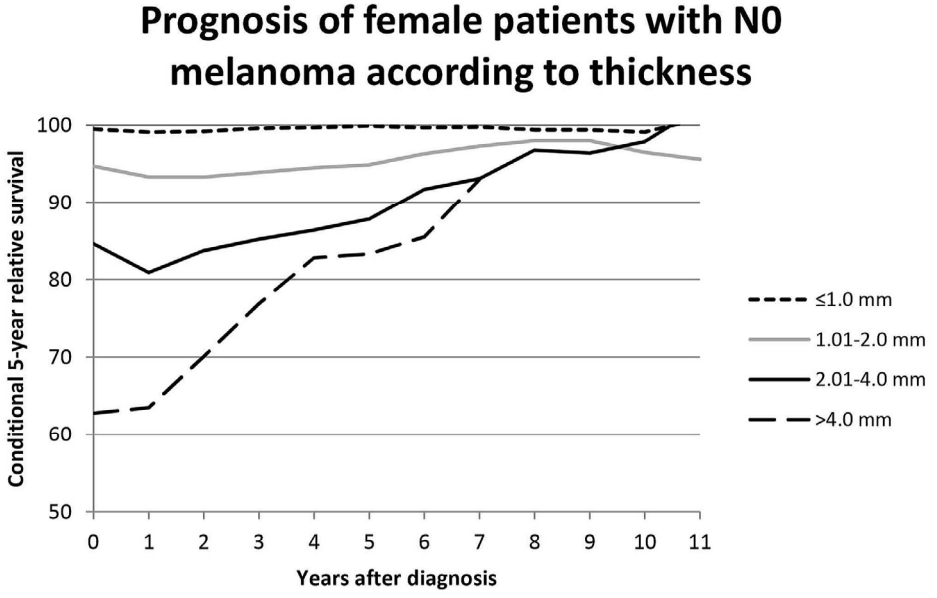

Figure 1b: 5-year relative survival at each time point after diagnosis for lymph node negative female patients who have already survived the previous year(s). Source: Netherlands Cancer Registry.

Table 2a. Conditional survival for male patients with melanoma in the Netherlands, 1994-2008 (n= 16,942)

	Breslow thickness	N stage	No. of patients available for conditional relative survival after year				Conditional 1- and 5-year relative survival (%)			
			0	5	10	Reliable estimate up to year[a]	At 0 years (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)	Years after diagnosis when there is minimal excess mortality[b]
1-yr CRS	**≤1.0mm (T1)**	N0	7,303	3,711	1,426	15	100 (100-100)	100 (99-100)	100 (99-101)	
		N+	84	34	12	6	91 (84-97)	95 (87-103)	-	
	1.01-2.0 mm (T2)	N0	3,429	1,595	545	15	100 (99-100)	97 (96-98)	98 (97-100)	
		N+	271	87	23	7	96 (93-98)	98 (94-102)	-	
	2.01-4.0 mm (T3)	N0	2,266	843	245	14	97 (96-98)	97 (95-98)	99 (97-101)	
		N+	483	123	18	8	93 (91-96)	91 (85-96)	-	
	>4.0 mm (T4)	N0	1,324	380	96	13	94 (92-96)	95 (92-98)	95 (89-101)	
		N+	446	76	26	9	86 (83-90)	94 (87-100)	-	
	Unk./missing	N0	847	643	410	15	100 (98-101)	96 (94-98)	100 (99-101)	
		N+	104	30	-	0	83 (76-91)	-	-	
5-yr CRS	**≤1.0 mm (T1)**	N0	4,390	1,792	315	11	99 (98-100)	99 (98-100)	100 (98-102)	0
	1.01-2.0 mm (T2)	N0	1,924	703	110	11	88 (87-90)	91 (89-93)	97 (92-101)*	8
	2.01-4.0 mm (T3)	N0	1,079	336	48	10	70 (68-73)	83 (79-87)*	93 (84-102)*	[c]
	>4.0 mm (T4)	N0	508	133	18	7	58 (54-61)	85 (78-91)*	-	[c]
	Unk./missing	N0	713	440	128	11	84 (81-87)	91 (88-94)*	98 (94-103)*	7

Abbreviations: 1-yr CRS, conditional 1-year relative survival; 5-yr CRS, conditional 5-year relative survival; CI, confidence interval; N0, no nodal involvement; N+, nodal involvement; n, number, Unk., unknown. Source: Netherlands Cancer Registry.

[a] Standard error ≤ 5% of survival rate

[b] Minimal excess mortality is defined as conditional 5-year relative survival >95%.

[c] Conditional 5-year relative survival >95% not reached within available follow-up period with reliable estimate for conditional survival.

[d] N0 includes patients with N0 and unknown N

* Significant improvement ($p<0.05$) in conditional 5-year relative survival with year survived after initial diagnosis.

Table 2b. Conditional survival for female patients with melanoma in the Netherlands, 1994-2008 (n= 23,108)

	Breslow thickness	N stage	No. of patients available for conditional relative survival after year				Conditional 1- and 5-year relative survival (%)			
			0	5	10	Reliable estimate up to year[a]	At 0 years (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)	Years after diagnosis when there is minimal excess mortality[b]
1-yr CRS	**≤1.0mm (T1)**	N0	12,217	6,863	2,734	14	100 (100-100)	100 (100-100)	100 (99-100)	
		N+	64	28	-	4	98 (94-102)	-	-	
	1.01-2.0 mm (T2)	N0	4,584	2,444	914	15	100 (99-100)	97 (96-98)	98 (97-100)	
		N+	280	119	25	9	98 (96-100)	96 (93-100)	97 (89-104)	
	2.01-4.0 mm (T3)	N0	2,296	1,084	342	14	99 (99-100)	95 (93-97)	99 (97-101)	
		N+	361	123	32	10	94 (91-97)	98 (95-101)	95 (87-104)	
	>4.0 mm (T4)	N0	1,096	368	92	13	95 (93-96)	96 (93-99)	98 (94-103)	
		N+	292	65	17	5	81 (76-86)	95 (89-101)*	-	
	Unk./missing	N0	1,254	1,148	841	15	99 (98-100)	99 (98-100)	100 (99-101)	
		N+	87	25	13	0	-	-	-	
5-yr CRS	**≤1.0 mm (T1)**	N0	9,761	3,427	586	11	100 (99-100)	100 (99-101)	99 (98-101)	0
	1.01-2.0 mm (T2)	N0	2,875	1,157	205	11	95 (94-96)	95 (93-97)	97 (93-100)	6
	2.01-4.0 mm (T3)	N0	1,320	456	121	11	85 (82-87)	88 (84-91)	98 (91-105)*	8
	>4.0 mm (T4)	N0	461	129	19	7	63 (59-67)	83 (76-91)*	-	[c]
	Unk./missing	N0	1,212	905	273	11	93 (91-94)	97 (95-99)*	99 (96-101)*	4

Abbreviations: 1-yr CRS, conditional 1-year relative survival; 5-yr CRS, conditional 5-year relative survival; CI, confidence interval; N0, no nodal involvement; N+, nodal involvement; n, number, Unk., unknown. Source: Netherlands Cancer Registry.

[a] Standard error ≤ 5% of survival rate

[b] Minimal excess mortality is defined as conditional 5-year relative survival >95%.

[c] Conditional 5-year relative survival >95% not reached within available follow-up period with reliable estimate for conditional survival.

[d] N0 includes patients with N0 and unknown N

* Significant improvement ($p<0.05$) in conditional 5-year relative survival with year survived after initial diagnosis.

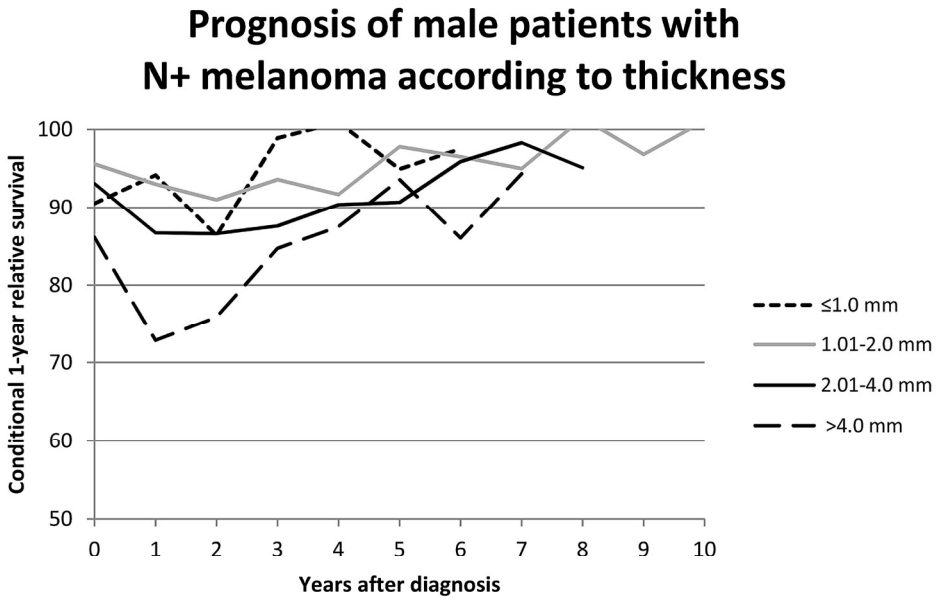

Figure 2a: 1-year relative survival at each time point after diagnosis for lymph node positive male patients who have already survived the previous year(s). Source: Netherlands Cancer Registry.

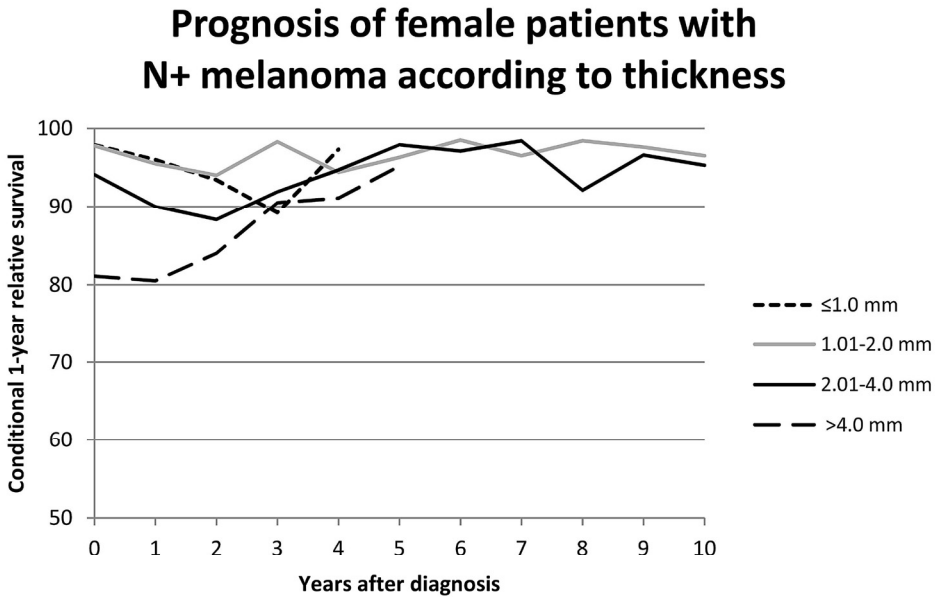

Figure 2b: 1-year relative survival at each time point after diagnosis for lymph node positive female patients who have already survived the previous year(s). Source: Netherlands Cancer Registry.

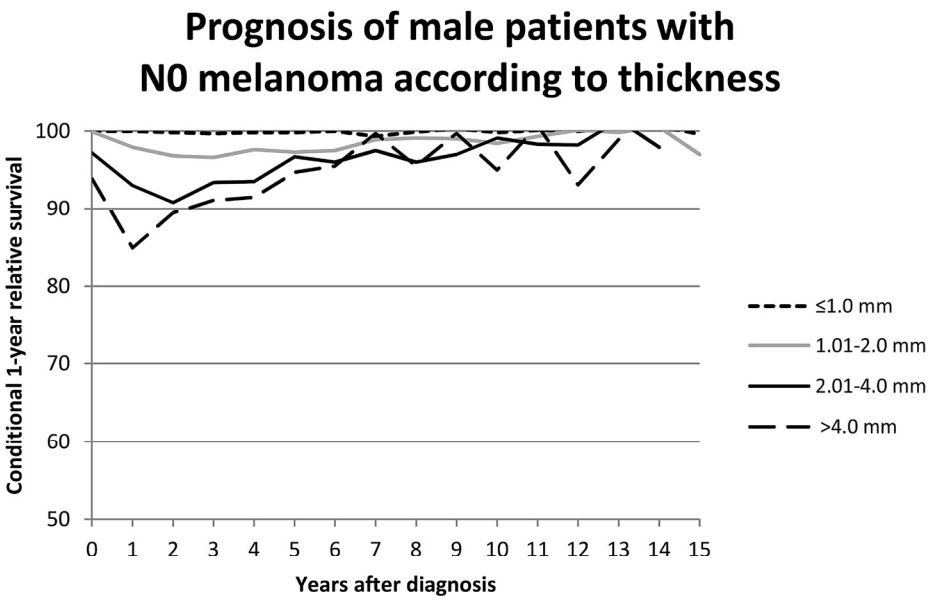

Figure 3a: 1-year relative survival at each time point after diagnosis for lymph node negative male patients who have already survived the previous year(s). Source: Netherlands Cancer Registry.

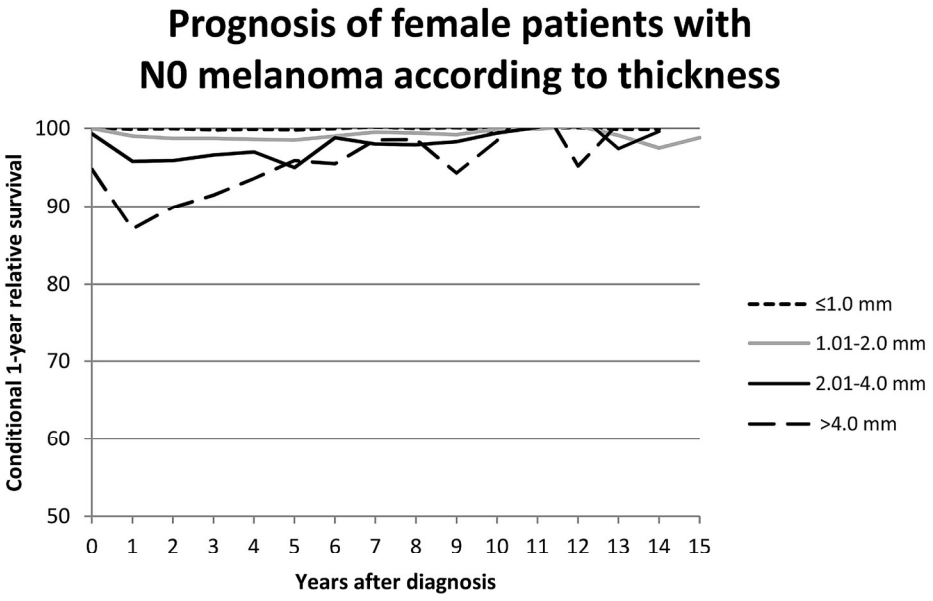

Figure 3b: 1-year relative survival at each time point after diagnosis for lymph node negative female patients who have already survived the previous year(s). Source: Netherlands Cancer Registry.

diagnosis. Minimal excess mortality for melanomas with a Breslow thickness of 1.01-2.0 mm (T2) was seen 8 and 6 years after diagnosis for males and females, respectively. For male patients with a 2.01-4.0 mm (T3) melanoma 5-year CRS increased from 70% (95%CI: 68-73%) at diagnosis to 93% (95%CI: 84-102%) 10 years after diagnosis (Table 2a). Among female patients, 5-year CRS increased from 85% (95%CI: 82-87%) at diagnosis to 98% (95%CI: 91-105%) 10 years after diagnosis. Minimal excess mortality was reached 8 years after diagnosis (Table 2b). Five-year CRS for both male and female patients with thick melanomas (T4, >4.0 mm) increased from about 60% at diagnosis to about 90% after 7 years. An excess mortality of around 10% remained (Figure 1a and 1b).

In female N+ patients with a 1-2mm (T2) thick melanoma the 5-year CRS was 80% (95%CI: 74-86%) at diagnosis and 83% (95%CI: 75-91%) 4 years after diagnosis. The 5-year CRS of female N+ patients with a 2-4 mm (T3) melanoma improved from 64% (95%CI: 58-70%) at diagnosis to 81% (95%CI: 74-89%) 3 years after diagnosis. The other subgroups with nodal involvement were too small for reliable 5-year CRS estimates.

Conditional 5-year relative survival analyses was also stratified for age groups, morphology and tumour location. No large differences in estimates were observed (results not shown), although a better CRS of superficial spreading melanomas was found compared to nodular melanomas.

For male patients with a superficial spreading melanoma 5-year CRS increased from 91% (95%CI: 90-92%) at diagnosis to 99% (95%CI: 97-100%) 10 years after diagnosis, in contrast with male patients with a nodular melanoma in which 5-year CRS increased from 67% (95%CI: 65-69%) at diagnosis to 93% (95%CI: 89-97%) 10 years after diagnosis. The 5-year CRS in female patients with a superficial spreading melanoma remained stable and comparable to the general population at diagnosis (97% [95%CI: 96-97%]) and 10 years after diagnosis (98% [95%CI: 97-99%]), in contrast with female patients with a nodular melanoma in whom 5-year CRS increased from 81% (95%CI: 79-83%) at diagnosis to 96% (95%CI: 93-99%) 10 years after diagnosis.

Conditional 1-year relative survival

A total of 2,503 patients (6%) had nodal involvement at diagnosis. The 1-year CRS at diagnosis for N+ male patients with a T1 melanoma of ≤1.0 mm (91%) and 1.01-2.0mm T2 melanoma (96%) was only slightly worse than N+ female patients with a melanoma of ≤2.0 mm (T1/2) where 1-year CRS at diagnosis was 98%. The short term prognosis fluctuated and improved slightly in male patients and remained stable in female patients. One-year CRS at diagnosis for N0 male and female patients with a melanoma of ≤2.0 mm (T1/2) was 100% and remained comparable to the general population during follow-up (97-100%) (Figures 2ab and 3ab).

In male N+ patients with melanomas with a Breslow thickness of >2.0 mm (T3/4) the 1-year CRS initially decreased fast and then increased up to 93% 5 years after diagnosis, in contrast with female N+ patients with >2·0 mm (T3/4) thick melanomas where 1-year CRS decreased slightly and increased up to 97% 5 years after diagnosis (Figure 2ab). In male and female N0 patients with >2·0 mm (T3/4) thick melanomas a similar declining trend of 1-year CRS was observed in the first 3 years after diagnosis and then improved to respectively 97% and 99% 10 years after diagnosis (Figure 3ab).

DISCUSSION

Survival of patients with advanced melanoma was fairly good 5 years after diagnosis. To the best of our knowledge, this is the largest population-based study providing accurate conditional survival estimates for melanoma patients according to gender, Breslow thickness, and nodal status with 1-year and 5-year CRS estimates up to 15 and 11 years after diagnosis, respectively. Dutch melanoma patients who are N0 at diagnosis and still alive 5 years after diagnosis have a high probability of surviving another 5 years (83-100%, depending on gender and Breslow thickness).

A large proportion of melanoma patients will survive their melanoma,[28] thus 5-year CRS estimates are an indication of a new prognostic model for melanoma survivors during follow-up. Studies on conditional survival may provide useful prognostic information for both patients and caregivers. We feel conditional survival is more useful for clinicians wanting to inform patients on their actual prognosis than the usual 5-or 10-year relative survival rates that are extremely influenced by patients who die rapidly after diagnosis and are not representative for the majority of the melanoma patients when they have survived a significant time since diagnosis.[1] The excess mortality function by time since diagnosis[10] is a good measurement to show what the prognosis is of patients then alive and when they might be 'cured'. In our study was shown that 5-year relative survival generally improved with time that patients have already survived. When such 5-year relative survival approaches 100%, that group of melanoma patients have a prognosis similar to the background population. The changing conditional 5-year relative survival rates for the various subgroups with time since diagnosis estimates accurately actual prognosis during follow-up. In this study estimates of excess mortality were only available for lymph node negative patients due to large enough sample size in this subgroup. To provide additional (short term) prognostic information to lymph node positive patients when they survived several years after the first melanoma diagnosis 1-year CRS was calculated.

Melanoma survival is substantially better for women than for men.[29-31] This was also reflected in the 1-year and 5-year CRS estimates for both N+ and N0 patients. We observed that minimal excess mortality was found in a later time period for men compared to women. In the short term prognosis curves of N+ T3/4 melanoma patients (2-4 mm/>4 mm) a faster rise was shown in the prognosis of female patients compared to male patients. This is in line with a study that found that female melanoma patients have a lower risk of disease progression compared to males.[30] The relatively good 5-year CRS of female N+ melanoma patients is a novel finding of major importance, which stresses the usefulness of CRS and could prevent long term anxiety amongst this group.

Three previous European studies provided CRS estimates for melanoma patients according to gender and age groups or country.[13-15] Gender and country influenced the estimates, while different age groups showed similar results in the different countries. Conditional relative survival was lower in countries with poorer survival rates.[14] Breslow thickness or stage were not available in these studies, therefore the minimal excess mortality estimates in these studies (3-7 years after diagnosis[15] and 5-7 years after diagnosis[13]) are rather negative for patients with thin melanomas, because N0 and N+ melanoma patients with varying tumour depths were analysed together.

A large U.S. study reported 5-year CRS for melanoma with local, regional, and distant disease at 0-5 years after diagnosis.[20] The 5-year CRS in localized melanoma remained stable (98% at diagnosis and 99% 10 years after diagnosis), an increase was found in regional melanoma (63% at diagnosis and 87% 10 years after diagnosis) and distant melanoma (15% at diagnosis and 80% 10 years after diagnosis).[20] The estimates of localized and regional melanoma correspond well with the 5-year CRS estimates of respectively T1(<1 mm) N0 melanoma in males and females, and T3(2-4 mm) N+ melanoma in females we found. Another U.S. study reported 5-year melanoma-specific and overall conditional survival estimates up to 5 years after diagnosis, which was stratified for stage, gender, and age groups.[17] The 5-year CRS for stage I was stable and comparable to the general population (97% at diagnosis and 98% 5 years after diagnosis), for stage II, III and IV an increase in 5-year CRS was shown (stage II: 72% at diagnosis vs. 86% 5 years after diagnosis, stage III: 51% vs. 87%; stage IV 19% vs. 84%).[17] These results (stage I-III) are comparable with 5-year CRS of respectively T1 (<1 mm) N0, T3 (2.01-4.0 mm) N0 in males or T3 (2.01-4.0 mm) N+ in females, and T4 (>4.0 mm) N0 in the present study. Patients younger than 50 years with stage II or III melanoma showed higher melanoma-specific 5-year adjusted conditional survival estimates than patients aged 50 years or older only in the first 2-3 years after diagnosis.[17]

Five year conditional disease specific survival of stage IIIA melanoma in the U.S. population was 78% at time of lymphadenectomy and increased up to 90% for 5 year survivors, for stage IIIB from 54% to 79% and for stage IIIC from 39% to 78%.[18] Another

U.S. study showed that 8 years after diagnosis no significantly different survival rates existed between high risk melanoma patients (T4N0M0 or T2-4N1-3M0) and low risk melanoma patients (T2-3N0M0)[19], supporting the minimal excess mortality of 8 years after diagnosis in T2N0 males and T3N0 females in this study.

A recent study concerning 5-year CRS of Australian cancer patients presented estimates for different stages of melanoma with results similar to ours.[16] The Breslow thickness categories and disease stages were grouped in four categories: localized, regional (Breslow thickness >2 mm (T3 and T4) were grouped with spread to regional lymph nodes), distant or unknown. The 5-year CRS in localized melanoma remained stable (99% at diagnosis and 99% 10 years after diagnosis), an increase was found in regional melanoma (74% at diagnosis and 99% 10 years after diagnosis) and distant melanoma (32% at diagnosis and 91% 10 years after diagnosis).[16] The different age groups (15-49, 50-69, and 70-89 years) in this study showed similar conditional survival.[16] The trends of this study were similar to those of our study, but comparing these studies is difficult, because different stratification categories were used (i.e. stage or melanoma spread vs. Breslow thickness and nodal involvement).

Conditional survival gives a quantitative estimate of the possibility of local or distant recurrence or a second tumour. Most recurrences and second primary melanomas are found in the first five years after the first melanoma diagnosis. However, this effect is not clearly visible in the 5-year CRS curves, since these patients had no nodal involvement and might be a more 'healthy' patient group with a lower risk of disease progression in the years after the melanoma diagnosis. The effect of recurrence or disease progression might be visible in the short term prognosis 1-year CRS curves (where a decrease was shown in the first years after diagnosis in almost all subgroups indicating a decreased survival in this time period).

Changes in sentinel node (SN) procedures and lymph node surgery might be responsible for misclassification of a part of the lymph node negative (N0) patients, since SN staging was not yet common practice in the Netherlands in 1994. SN staging has become more or less routine practice nationwide during the first decade of the 2000's. The NCR records N stage only at the time of first diagnosis. Thus, in the pre-SN era, it only recorded patients with simultaneous palpable (macrometastases) lymph node metastases. Therefore, a number of N0 patients was understaged, since occult (micro) metastases were not detected, because no SN procedure was performed.

Strengths of this study are the size of the population-based cohort, completeness of the cancer registry data, length of follow-up time, and stratified CRS rates based on three important prognostic factors (gender, Breslow thickness, and nodal involvement). The better CRS of superficial spreading melanomas compared to nodular melanoma could

be explained by the fact that nodular melanomas have a higher Breslow thickness than superficial spreading melanomas. These results are reflected in the stratified Breslow estimates. Limitations are the lack of power to calculate 5-year CRS estimates for most subgroups of patients with nodal involvement and the merged group of lymph node positive patients (N1-N3) in the 1-year CRS estimates. The short term prognosis estimates of 1-year CRS showed fluctuations and had wide confidence intervals and is therefore more difficult to use in clinical practice than 5-year CRS estimates.

In conclusion, the prognosis for melanoma survivors improved with each additional year of survival after initial diagnosis (except for patients with ≤1 mm T1 melanomas who already showed minimal excess mortality at diagnosis). In the first years after diagnosis there were large improvements in conditional survival for melanoma patients, especially with a Breslow thickness of >2mm (T3/4) and female patients who were lymph node positive. Quantitative insight into conditional survival is useful for dermatologists, surgeons and oncologists to help planning optimal cancer surveillance. It gives a more optimistic message of their future to melanoma survivors than the traditional survival rates and could reduce anxiety concerning their melanoma diagnosis in the past.

ACKNOWLEDGEMENTS

This research was performed within the framework of the project 'Insight into health aspects of long-term cancer survivors in the Netherlands – a tool for caregivers and cancer survivors' (Dutch Cancer Society Grant IKZ 2009-4316).The funding source had no involvement in data collection, data analysis and data interpretation.

We thank the registrars of the Netherlands Cancer Registry for their dedicated data collection. We thank Arjen Joosse for his critically reading of the manuscript and useful comments.

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SUPPLEMENTAL DATA

Year of diagnosis	Year of follow-up															
	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
1994	1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	11/12	12/13	13/14	14/15	15/16
1995		1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	11/12	12/13	13/14	14/15
1996			1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	11/12	12/13	13/14
1997				1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	11/12	12/13
1998					1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	11/12
1999						1	1/2	2/3	3/4	4/5	**5/6**	6/7	7/8	8/9	9/10	10/11
2000							1	1/2	2/3	3/4	**4/5**	**5/6**	6/7	7/8	8/9	9/10
2001								1	1/2	2/3	**3/4**	**4/5**	**5/6**	6/7	7/8	8/9
2002									1	1/2	**2/3**	**3/4**	**4/5**	**5/6**	6/7	7/8
2003										**1**	**1/2**	**2/3**	**3/4**	**4/5**	**5/6**	6/7
2004											**1**	**1/2**	**2/3**	**3/4**	**4/5**	**5/6**
2005												**1**	**1/2**	**2/3**	**3/4**	**4/5**
2006													**1**	**1/2**	**2/3**	**3/4**
2007														**1**	**1/2**	**2/3**
2008															**1**	**1/2**

Supplemental Figure 1: Years of diagnosis and years of follow-up included in the calculations of hybrid estimates of 5-year relative survival of patients for the years 2004-2009. The numbers within the cells indicate the years following diagnosis.

See http://www.sciencedirect.com/science/article/pii/S095980491300957X.

Part III

Survival

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CHAPTER 10

Comparing survival of patients with single or multiple primary melanoma in the Netherlands: 1994-2009

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Part IV

Discussion

CHAPTER 11

Discussion

Multiple cutaneous (pre)-malignancies: old news or time for action, to treat or not to treat (in some cases), to follow or to not follow? In order to provide a contribution to these debates, this thesis provides insight into the occurrence and survival of multiple cutaneous (pre)-malignancies using several data sources and analyses. These include two systematic reviews and meta-analyses, five population based cohort studies and a population-based cross-sectional study. In this discussion chapter, I will first answer the research questions posed in the introduction of this thesis briefly and present the limitations of the studies. Finally, I will discuss possible implications and recommendations for future perspectives.

Part I: What are the risks of developing multiple cutaneous (pre)- malignancies (melanoma, SCC and BCC)

a. in The Netherlands, and

b. worldwide (Europe, North America and Australia)?

The risks for the Netherlands were evaluated using data of the population-based Netherlands Cancer Registry and Eindhoven Cancer Registry, which provided data of first and subsequent skin cancers of Dutch patients diagnosed with melanoma, SCC and BCC. These studies show that the risk of developing a subsequent skin cancer after a first melanoma, SCC or BCC is significantly elevated on the short- and long-term. The SIR of a subsequent different skin cancer ranged between 3 and 6 and SIR of a melanoma after melanoma ranged between 12 and 26. The 20-year cumulative risks varied largely between the different tumor combinations (1-28%).

To investigate the risks on a global level, an extensive systematic literature search was conducted (last performed on January 18, 2012). A history of a prior melanoma was shown to be a strong predictor for development of a subsequent melanoma (approximately 10-fold increased risk) and to a lesser extent SCC or BCC (3 to 5 fold increased risk). A history of a prior KC is a very strong predictor for developing a subsequent SCC and BCC (range pooled SIR 3-17, range pooled proportion 4-29%) and to a lesser extent melanoma (pooled SIR approximately 2.5 and pooled proportion 0.5%).

This information on risks for subsequent skin malignancies could serve as information for patients, doctors and health care systems in explaining the importance of skin self examination, and planning follow-up care, amongst others.

Part II: a.) What are the trends in incidence of thin melanomas and b.) what is the prevalence of actinic keratosis in The Netherlands?

To evaluate if there are indications of overdiagnosis, we investigated time trends of incidence of thin melanomas. The incidence rates of in situ, thin and thick melanomas increased in a similar pace between 1994 and 2010 (source data: Netherlands Cancer Registry). However, for in situ melanomas and thin melanomas, increases were more

marked in recent years, in men. These recent accelerations in the increasing trends for thin and in situ melanomas are most likely caused by a combination of increased ultraviolet exposure, increased awareness, early detection and 'overdiagnosis' and therefore a mixture of an artificial and a true increase.

At the time of initiation of this thesis, there was no data available on the prevalence and risk factors of actinic keratoses in The Netherlands. The prevalence of actinic keratosis is very high (49% for men and 28% for women), especially among elderly bald males (OR 6.3 in patients with >10 AK) (source data: Rotterdam Study). As AKs may progress to invasive SCC, the prevention and management of AK is a true challenge for patients, physicians, and health-care policymakers, particularly considering this very high prevalence in the population.

Part III: What is the conditional survival of lymph node negative and positive melanoma patients and patients with multiple melanoma?

The increasing incidence and relatively good survival, have resulted in a growing group of melanoma survivors. Conditional survival is a method to estimate the survival rate of patients who already survived a certain period of time. I found that with each additional year that Dutch melanoma patients survive after their diagnosis, their prognosis improves, except for patients with a melanoma thinner than one millimeter, who never had any excess mortality during follow-up. Six to eight years after diagnosis, survival of patients with a T2 melanoma was equal to that of the general population, and conditional 5-year relative survival for T4 patients increased from 60% to 90% at 7 years after diagnosis. Conditional survival of melanoma was better amongst females (as expected[1,2]), amongst those with lower Breslow thickness and nodal stage. Conditional survival estimates generally give a more optimistic message to patients who have already survived a certain amount of time compared to the traditional survival rates.

Survival of multiple melanomas was better than single melanomas in regular Kaplan Meier curves and conditional survival estimates. If the time between melanomas was taken into account in a Cox proportional hazards model as a time dependent variable the hazard ratio of multiple versus single melanoma was higher.

MULTIPLE CUTANEOUS (PRE)-MALIGNANCIES

It is not new that the risk of developing a subsequent cutaneous malignancy after an initial skin cancer is increased. Fred Wise, professor of Dermatology and Syphilology, already discussed in 1929 that multiple epitheliomas (keratinocyte carcinoma and precursors) are certainly not relatively 'benign', and mentioned the metastatic potential of prickle cell growths and (more rarely) basocellular neoplasms[3]. Almost 100 years after

this observation, skin cancer has become a major public health problem due to increasing incidence rates and occurrence of multiple cutaneous (pre)-malignancies. Recently, a U.S. study reported a substantial increase in average annual total cost for skin cancer from 3.6 billion dollar in the period 2002-2006 to 8.1 billion dollar between 2007 and 2011, representing an increase of 126.2%, while the average annual total cost for all other cancers (excluding skin cancer) increased by 25.1%[4]. These findings emphasize the importance of skin cancer in (public) health policy, as well as the urge for effective primary and secondary prevention. Early detection and possible overdiagnosis will further increase the economic burden of skin cancer but should result in decreasing mortality rates. The recently stabilizing mortality rates of melanoma in The Netherlands[5] indicate the first advantages of early detection and increased awareness, and less likely may also have been caused by new targeted therapies.

Skin cancer and premalignant skin lesions sometimes cause confusion to doctors and patients, because a (skin) cancer diagnosis might cause feelings of distress and anxiety among patients[6] whereas doctors or dermatologists might explain their diagnosis rather casually because of the generally good prognosis. Doctors know some lesions (e.g. AK or BCC) are rather meaningless, but treat them anyhow because the course of the individual lesion is unknown. Some patients are able to self-examine their skin and accept discharge from further clinical follow-up, other patients prefer a lifelong annual full body skin examination by their dermatologist. Aging of the population and lifestyle habits (e.g. sun seeking behavior) increases the number of patients, a proportion of them geriatric, with (extensive) actinic damage and (multiple) cutaneous (more advanced) malignancies. Dermatologists should be aware of the overall elderly patients' general health status both physically and cognitively, and short-term as well as long-term goals. When it comes to patients' autonomy, the ability of elderly patients to make their own decisions regarding their health care should be evaluated and, if needed, appropriate family members or caregivers should be involved in the decision-making processes[7]. Less costly treatments (e.g. curettage or cryotherapy) with higher recurrence rates and a poorer cosmetical outcome may on the long term lead to higher health care costs (if the geriatric patient survives and Mohs' micrographic surgery is required to treat of a recurrent skin cancer). On the other hand, if the remaining life expectancy of the patient is limited, watchful waiting without intervention may be appropriate. Of course, evaluation of the patients' appearance and sense of well-being and attractiveness and potential limitations in application of topical treatments is needed equally for geriatric as other patients[7]. The rising group of ageing patients with a comorbidity interfering with surgery might indicate symptomatic treatments of extensive BCCs, AKs, SCCs or lentigo maligna's rather than curative treatments (palliative purposes versus curative care according to Internal Oncology); literature on this topic in the field of Dermato-Oncology is scarce.

LIMITATIONS OF THE STUDIES WITHIN THIS THESIS

The major limitation of the meta-analysis (**chapter 2 and 3**) was the lack of information of high quality risk estimates (SIR). We had to focus mostly on "proportion" as risk estimate because the majority of studies investigating KC patients reported only proportions. The preferable SIRs, which control for background incidence or cumulative risk, is time-specific and accounts for the competing risk 'death' were hardly reported in existing literature. Cancer registries mainly report the first histologically confirmed BCCs and SCCs. Therefore the risk of a subsequent BCC or SCC could only be calculated for very few populations using population-based data. Available data were primarily from smaller hospital-based studies, with shorter follow-up and a potential of selected populations, that may have underestimated the pooled proportions. A (relatively limited) part of the BCCs are clinically diagnosed (proportion in The Netherlands 7.1% vs. Scotland, Finland and Malta 0.7% - 24.1%[8]), which may further underestimate the pooled proportions and SIRs. Also, the on average younger age of melanoma patients compared to patients with a KC, together with limited follow-up time could have influenced the pooled BCC or SCC risk negatively.

Generally, as the number of follow-up visits increase, so does the number of subsequent skin cancers detected and therefore the proportion (i.e. surveillance bias). The averaged cumulative risks were based on a few studies and therefore external validity of these measurements is rather limited.

The high risks of subsequent melanoma, BCC or SCC in patients with melanoma or KC described in **chapter 4 and 5** might be related to increased patients' and doctors' awareness illustrating selection bias and length-time bias[9] (i.e. slowly growing tumours are more likely to be discovered). In the case of subsequent melanoma, some benign lesions that are misclassified as melanoma could result in some melanoma overdiagnosis, because of the difficult histological interpretation of very small melanocytic lesions from patients with a history of melanoma[10]. However, the main objective of increasing awareness is early detection and a decrease of melanoma mortality. Anyhow, increased surveillance and early detection will result in increasing numbers of melanoma with a good prognosis, and therefore the term overdiagnosis might be inappropriate. Recently the term indolent lesion of epithelial origin (IDLE) was introduced, and the need for a new terminology for several indolent (pre)-cancers was suggested[11]. The increased risk of a subsequent skin cancer, either of the same or a different type, might be caused by field cancerization and other shared risk factors, although individual effects are difficult to examine. Further limitations of these studies are the absence of information concerning phenotypic characteristics of patients, lifestyle and behavior, medication use such as immunosuppressive drugs and genetic susceptibility, which are all related to individual risks of developing one or more skin cancers.

A limitation of the study of trends in incidence of thin melanomas (**chapter 7**) is the proportion of patients with a missing Breslow thickness. As the regional comprehensive cancer center in Rotterdam began capturing information regarding Breslow thickness on a routine basis later than the other regional comprehensive cancer centers, we decided to exclude this registry from the analyses. Further limitations are the unknown levels of a true increase, increased awareness, diagnostic drift and overdiagnosis. I believe all play a role to a certain extent but based on the available data we were not able to discern which proportion each effect contributed. The difficult interpretation of small melanoma simulators and small in situ or micro-invasive melanomas causes misinterpretation[10] of indolent lesions. Diagnostic drift seems to have occurred, supported by the observation that a re-evaluation of biopsy specimens taken 20 years ago results in a higher number of melanoma diagnosis (approximately 25% of 29 dysplastic nevi diagnosed between 1988 and 1990 were diagnosed as melanoma between 2008 and 2009) recently compared to 20 years ago[12]. The increased use of dermoscopy and identification of more atypical small lesions (which could be harmless and not affect life expectancy) might further increase the wanted early detection or possibly unwanted overdiagnosis.

The clinically diagnosed actinic keratoses in The Rotterdam Study (**chapter 8**) may have led to misclassification and an underestimation or overestimation, because AK can resemble keratinocyte carcinoma. However, nondifferential misclassification was estimated to be small, considering previously reported positive predictive values of a clinical AK diagnosis ranging from 74% to 94%[13,14]. Moreover, the use of categorized data (1-3, 4-9, ≥ 10 AKs) decreased the inter-observer variation[15]. The cross-sectional design and missing information concerning previous treatment of AK are further limitations to this study. However, prevalence data are by definition cross-sectional, and in a future measurement of the Rotterdam Study we can evaluate trends of the occurrence of AKs.

The lack of power to calculate 5-year conditional relative survival (CRS) estimates for most subgroups of patients with nodal involvement was a limitiation of the study in **chapter 9**. The fluctuations with wide confidence intervals in the short term prognosis estimates of 1-year CRS makes these numbers less appropriate for use in clinical practice. Limitations of the complex analysis of survival of multiple malignancies (**chapter 10**) are: the relatively small subgroup of patients with multiple melanomas, limiting stability of estimates and stratification of different subgroups with a different Breslow thickness. Particularly the fact that being classified as patient with multiple melanomas already implied that a patient survived the time between first and second melanoma diagnosis, caused methodological problems to circumvent in order to provide valid estimates and conclusions.

POSSIBLE IMPLICATIONS AND RECOMMENDATIONS FOR FUTURE PERSPECTIVES

I Individual patient – Clinical relevance

The increasing number of (multiple) cutaneous (pre)-malignancies in The Netherlands requires improvements in primary and secondary prevention. *Primary prevention* of skin cancer is a challenge, because protection against exposure to ultraviolet radiation requires environmental changes (e.g. create shade by planting trees, reschedule work practices and sporting times), social changes (sun bathing habits and solarium use for a cosmetic tan) and most of all behavioural modification (sunscreen use, wearing hats and long-sleeved clothes) and policy changes (a sunbed ban). Even though instructions for behavioural modifications are clear, it is notoriously difficult to change these types of habits. Moreover, in practice, it seems that a proportion of the population uses sunscreen in order to be able to stay in the sun for longer periods. The interaction of skin cancer and ultraviolet protection knowledge, attitudes towards tanning and ultraviolet protection behaviour needs further investigation[16].

In 1989, a screening campaign for skin cancer was organized using a 'freckle bus' for skin examinations in four seaside resorts of The Netherlands. Much publicity was given to the campaign by the (inter)national media and it appeared that after the campaign there was an increase in the number of consultations and diagnoses of malignant lesions. A similar education and screening campaign was organized in Belgium in 1999 ('Melanoma day') and since 2000 it is active in a large and growing number of European countries under the name Euromelanoma[17]. Since 2013 a national skin cancer day is organized annually in May in The Netherlands (www.huidkanker.pro) to increase awareness and several hospitals offer free skin examinations by dermatologists. To improve efficacy of prevention campaigns, high risk populations must be reached such as elderly men and people with lower socio-economic status that usually escape campaigns[18]. In Australia, since 1980 many public health campaigns and environmental interventions were used to stimulate sun protection. These campaigns should have decreased the incidence of melanoma in younger populations that were born and raised during the active campaigns, however, the crude rate of melanoma in patients under 30 years of age in the susceptible population (total number of Australians minus Australians born in Asia, the Pacific Islands, the Middle East, or sub-Saharan Africa; and Australian-born children whose parents were born in these regions) increased from 5.9 per 100,000 in 1982 to 6.3 in 2009[19]. On the other hand, mortality rates are decreasing in younger patient groups. One of the secrets behind the relative success of this campaign is that prevention programmes are hosted by a stable and supportive organization with reliable funding for about 30 years[20].

Secondary prevention of skin cancer consists of early detection and is obtained by increased surveillance by the population at risk and their physicians. Routine skin self-

examination increases chances of early detection and treatment and may be the key to better survival, particularly in the case of melanoma. Sensitivity of skin self-examination (SSE) for melanoma is low (25-93%, patients are often unable to count the number of nevi or detect atypical nevi and changes in mole size on their own bodies correctly), specificity is higher (83-97%), future studies to improve its accuracy are needed, because SSE would be the easiest screening-tool[21]. Different types of images used in educational aids have improved the performance of skin self-examination and the accuracy of SSE and melanoma detection[22]. Several studies are underway using apps for the smartphone, either with or without tele-evaluation by experts[23-25]. Early detection by physicians (other than dermatologists) may improve by optimizing skin cancer examination education at medical school and identifying curricular factors associated with medical students' confidence, intent, and performance regarding the skin cancer examination[26]. Data concerning true effects on morbidity and mortality of self-examination and effects of regular examination of the skin by a general practitioner, nurse practitioner or by even the patients' partner or significant other who has received a training is absent[27]. Most studies investigating mobile teledermoscopy have been small pilot cohort studies or trials, larger studies investigating a representative group of patients (including those with little technical skills) are needed to confirm the viability[28].

Reasons for *follow-up* (or *tertiary prevention*) of skin cancer patients include detection of a recurrence, diagnosis of second primary skin cancers and provision of psychosocial support and/or information. The majority of recurrences of skin cancer are found in the first years after initial diagnosis, but as I have shown, the risk of subsequent skin cancers remains elevated lifelong. Skin cancer follow-up in The Netherlands is quite limited according to the guidelines[29-31] and patients' perspective has not been included in determining the cut-off. Anyhow, patients with extensive actinic damage, high numbers of (atypical) moles and immune suppressed patients are advised annual follow-up visits. The subgroup with extensive actinic damage needs a more clear definition (e.g. >10 actinic keratosis and/or >3 keratinocyte carcinomas in medical history). In patients with localized melanoma less intensive monitoring might lead to more efficient follow-up strategies[32]. A subset of patients with KC may not develop another KC, a better understanding of the course and frequency of subsequent KC might improve follow-up strategies[33]. At this moment no evidence-based data is available concerning frequency and duration of follow-up of melanoma and keratinocyte carcinoma and I suggest a clinical trial comparing annual skin examinations of high risk populations by a dermatologist/general practitioner versus skin cancer education of patients.

Large-scale skin cancer screening is not recommended by the US Preventive Services Task Force[34]; modelling studies suggest that selective targeted screening might be a more cost-effective strategy[35]. The identification of high risk populations may be improved by *risk prediction models*. Recently, a systematic review was reported which

described and compared 25 risk prediction models for melanoma[36]. The 25 risk prediction models considered 144 different possible risk factors, which included 18 measures of number of naevi, 26 of sun / ultraviolet exposure, 14 of history of sunburn and the risk factors which most likely remained in the final model were age, number of naevi, presence of freckles, history of sunburn, skin type, hair colour, skin colour and personal history of skin cancer. Fourteen studies provided discriminatory performance estimates with values for the area under the receiver operating curve (AUROC) of approximately 0.76 with little difference between models for self-assessment and those requiring a health care professional; only two models have been validated in separate populations with AUROC values of 0.79 and 0.70[36] . More studies validating existing models and development of new risk models incorporating genetic information were suggested. Olsen et al[37] recently assessed the performance of six melanoma risk prediction tools in two independent data sets, 762 melanoma cases and a population-based sample of 42,116 people without melanoma, and found that most existing prediction models were poorly calibrated. However, most models had reasonable discriminatory accuracy (AUROC 0.73-0.93)[37]. Problems to estimate cancer risk at the individual level are a) that the primary risk factors are common in the population, b) effects of risk factors are typically modest (relative risks < 5) and do not discriminate those who will develop cancer from those who will not, and c) most cancers have long latent periods and arise in individuals with a risk close to the general population[38]. The addition of integrating genetic risk profiles to models in breast cancer only modestly improved discrimination (AUROC for a risk model with age, study and entry year, and four traditional risk factors was 58.0%; AUROC with addition of 10 genetic variants was 61.8%)[39].

Several studies suggested a *chemopreventive effect* of non-steroidal anti-inflammatory drugs (NSAIDs) for cancer, however a recent Dutch study[40] and recent meta-analysis[41] do not support these findings in the case of melanoma and keratinocyte carcinoma. Transplant recipients showed a reduced risk of new keratinocyte carcinoma when acitretin was compared to placebo (relative risk 0.22) without significant differences in risks of adverse events and T4N5 liposome lotion significantly reduced the rate of new BCCs in xeroderma pigmentosum patients, however the number of trials is small and studies show inconsistent results[42]. Chemoprevention for (multiple) cutaneous (pre)-malignancies is an interesting strategy that needs to be explored further in observational and interventional studies which investigate the risk-benefit ratio of the candidate drug[43].

II Societal impact

The high incidence of (multiple) cutaneous malignancies combined with a relatively good prognosis (more than 90% of skin cancer patients survives) results in a large and growing group of skin cancer survivors. In 2005, the Institute of Medicine noted in a report that many cancer survivors become lost in the transition from cancer patient to

cancer survivor and recommended recognizing cancer survivorship as a distinct phase of cancer care that deserves ongoing attention from cancer and other health care providers, however, the specific challenges that individual survivors encounter vary widely[44]. The first step of a *survivorship care plan* is the treatment summary, the next step is the ongoing care plan for survivors with a clear plan for the patient and all involved health care providers including guidelines for surveillance of development of recurrence or new cancers, long-term and late effects of treatment (e.g. cosmetic scarring from surgery), noncancer health care and health maintenance (specific recommendations on lifestyle issues), psychosocial concerns (simple recognition and referral can be enough to improve psychosocial outcomes in many cases), employment/insurance/economic issues and identification of providers (which provider will be responsible for ongoing cancer monitoring)[44]. In the Netherlands melanoma survivors received more follow-up than recommended by the Dutch melanoma guideline[45], which might be caused by patients' need for additional care or doctors' preferences. Future research should focus on the different elements of a proposed survivorship care plan (diagnosis, previous treatments, plan for surveillance and monitoring, resources available, and correct providers for different problems), evaluating levels of satisfaction, variations in follow-up practice patterns and outcomes, testing the acceptability of survivors and providers who use different models or survivorship care and determining the current and optimal levels of involvement of different specialists and primary care physicians in the creation and execution of the survivorship care plan[44]. Cost and time restraints are major barriers for the creation and use of survivorship care plans, and the expectation that electronic medical records can simplify and accelerate survivorship care plan development is yet to be achieved[46].

The high incidence of skin cancer also has imposed an increasing burden on *primary health care* in the Netherlands and most likely health care costs as well (total number of contacts for malignant skin lesions had an annual percent change of +11.8% between 2001 and 2010[47]). Since 2006, in 31.2% of 4,513 patients that had a first visit for a skin lesion suspected of malignancy, general practitioners performed minor surgery within one year after their first contact and in total 13.0% of the patients were referred for specialized care (data from general practice registration network in the northern part of the Netherlands with an average annual population of approximately 30,000 patients)[47]. A study in Australia investigated number of lesions needed to excise or biopsy (NNE) for 1 melanoma or 1 nonmelanoma skin cancer to be detected and found that the NNE for melanoma and nonmelanoma skin cancer in primary care physicians were respectively 1.5 and 19.6 with strong effects of clinical impressions and patients pressure to excise[48]. General practitioners and skin cancer clinic doctors in Queensland treat large numbers of melanomas and keratinocyte carcinoma and diagnose these skin cancers with high sensitivity[49]. At this moment the Dutch skin cancer guidelines are quite vague about the

different roles of health care providers (third line versus second line (and dermatologist versus [surgical] oncologist) versus first line/general practitioners) during follow-up[29-31]. Future research should evaluate the role and quality of dermatologists and general practitioners in skin cancer diagnosis, treatment and follow-up. In 2013, a relatively small faculty of 538 dermatologists and a large faculty of 11,192 general practitioners were registered in the Netherlands[50]. Future research needs to focus on health care capacity and costs (available time dermatologists, general practitioners and nurse practitioners). Depending on offer and demand, a shift of a part of skin cancer care towards first line care might cause loss of income and employment of dermatologists. Such a shift may also lead to an improved quality of care and higher patient satisfaction if patients prefer to go to the GP and the dermatologist has more time for difficult cases. A high quality capacity, quality and cost-effectiveness study of skin cancer care should further investigate this sensitive issue.

In the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany SCREEN project (SCREEN), 360,288 inhabitants received at least one whole-body examination [participation rate women 27% and men 10%, 75% of screenees were women]. The examination was performed by general physicians, the screenee was referred to a dermatologist if a suspicious lesion was detected. Screenees were also free to consult a dermatologist for initial screening, but only 22.6% used that pathway. The study presented evidence that the skin cancer screening program produced a nearly 50% reduction melanoma mortality in Schleswig-Holstein[51,52]. However, the fast decline in mortality rates could also be caused by increased awareness or diagnostic or treatment effects. The SCREEN project had a substantial impact on melanoma incidence[53] and caused high numbers of excisions in the youngest screenees with an associated low yield[54]. Also a pronounced incidence increase was found for BCC and SCC which might improve early detection and treatment and hopefully reduce recurrences and costs, but it could not ruled out that screening might increase morbidity and costs (if detected lesions would otherwise not have been noticed during patient's lifetime)[55]. Worldwide no other countries followed the German example of mass screening and the benefit-risk ratio of skin cancer screening remains unknown[56]. The small number of dermatologists in the Netherlands and shrinking health care budgets would never allow examination of all Dutch inhabitants similar to the German model. I therefore suggest validation studies of the previously mentioned risk prediction models to create possible (cost-effective) targeted screening strategies.

Information provision in the Netherlands needs a Dutch web-based tool/ a smartphone app and skin cancer patient brochure (for older patients) to better inform skin cancer survivors about the different aspects of skin cancer (risk of recurrence/second primary skin cancer, prognosis at time of diagnosis and during follow-up, monthly skin-self-examinations and sun protection recommendations). Psychological distress should

be evaluated with a short questionnaire (or visual analogue scale) during a follow-up visit, if distress is high an educated nurse or general practitioner should be involved in distress management. I suggest lifelong annual follow-up visits for patients with >1 melanoma (in situ), >3 keratinocyte carcinomas or >10 actinic keratosis, because of the high level of actinic damage and/or field cancerization. Skin cancer risk reduction (sun protection, ban solariums, education material with images of early signs of skin cancer vs. advanced skin cancer and benign lesions, skin self-examination instructions and awareness campaigns) needs to improve in The Netherlands.

CONCLUSION

The increasing incidence of multiple cutaneous (pre)-malignancies in The Netherlands is and remains a large burden for the current health care system and will only increase in the future. This thesis contributes to the current knowledge on the occurrence of multiple cutaneous malignancies and associated mechanisms of field cancerization and overdiagnosis and could therefore be used as material for patient education and follow-up strategies. More research is needed in the field of treatment choices and all stages of prevention to manage skin cancer optimally. Mechanistic studies investigating aetiology and genetics are needed to further reduce the burden of multiple skin cancers. Cost-effectiveness studies are required to reduce the pressure of skin cancer on the Dutch health care system and I suggest further studies investigating the role of different health care providers in the first, second and tertiary line in terms of diagnosis, treatment and follow-up.

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Part IV

Summary

CHAPTER 12

Summary
Samenvatting

Summary

Chapter 1 is a general introduction to this thesis. Skin cancer, the most commonly occurring cancer in Caucasian populations, includes a large number of types of malignancies deriving from a myriad of different cells. The three most common cutaneous malignancies are derived from melanocytes and keratinocytes (ordered in decreasing aggressiveness): melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). This thesis focuses only on these three types of cancer and their precursors. The incidence rates of the three most common skin cancers are rising and show large variations between countries. The majority of skin cancer patients have a relatively good prognosis, which has implications for treatment, follow-up strategies and risks of developing multiple cutaneous (pre)-malignancies. Important topics like follow-up and early detection of skin cancer remain a subject of debate. In this thesis I describe the burden of multiple cutaneous malignancies and their consequences for patients, doctors and health care systems.

In **chapter 2** a systematic review and meta-analysis is performed to investigate risks (i.e. proportions, standardized incidence ratios [SIR] and cumulative risks) of developing a melanoma, basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) after a melanoma. Fifty, of 233 fully read articles, met selection criteria. In melanoma patients, pooled proportions for a subsequent melanoma, BCC or SCC were respectively 3.8% (n=47), 2.8% (n=5) and 1.0% (n=6). The pooled SIRs for a subsequent melanoma, BCC or SCC in melanoma patients were respectively 10.4 (n=12), 4.6 (n=2) and 2.8 (n=2). Mean 20-year cumulative risks of a subsequent melanoma, BCC or SCC in melanoma patients were respectively 5.4% (n=3), 14.0% (n=1) and 4.0% (n=1). Subgroup analyses showed substantial differences in reported risks between continents and study design. In conclusion, a history of a prior melanoma is a strong predictor for development of a subsequent melanoma (approximately 10-fold increased risk) and to a lesser extent BCC or SCC. This information could serve as information for health care systems. Further, secondary prevention seems pivotal in this patient group.

In **chapter 3** a systematic review and meta-analysis is performed to investigate the risk (i.e. proportions, cumulative risks or standardized incidence ratios [SIR]) of a subsequent basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma in patients with a previous keratinocyte carcinoma (KC; including BCC and SCC). In total, 45 articles fulfilled the inclusion criteria. In BCC patients, the pooled proportion for a subsequent BCC, SCC or melanoma was respectively 29.2%, 4.3% and 0.5%. The pooled proportion

of a subsequent SCC, BCC or melanoma in SCC patients was respectively 13.3%, 15.9% and 0.5%. The pooled SIRs for a subsequent BCC, SCC or melanoma were respectively 17.4, 3.2 and 2.4 in BCC and 4.2, 15.0 and 2.7 in SCC patients. In the subgroup analyses, strongest differences in risks were found in the continent strata (risks Australia>North America>Europe). A history of a prior KC is a very strong predictor for developing a subsequent BCC and SCC and to a lesser extent melanoma. Secondary prevention (early detection of subsequent episodes of the disease) is pivotal in patients with a prior KC. Patients should be well informed about future risk and require adequate follow-up by physicians.

In **chapter 4** we estimate risks (cumulative risks, standardized incidence ratio [SIR] and absolute excess risk [AER] of developing a second primary in situ or invasive cutaneous melanoma after a first melanoma in The Netherlands, between 1989 and 2008. In total, 10,765 in situ and 46,700 invasive melanoma patients were included (source: Netherlands Cancer Registry). Cumulative risks of a second invasive melanoma after a first in situ or invasive melanoma at 20 years of follow-up were 6.2% and 5.0%, respectively. Relative risk of developing any melanoma (in situ or invasive) after any first melanoma (SIR) was 12.4 (invasive after invasive melanoma) to 26.4 (in situ after in situ melanoma) fold increased compared to the general population. SIRs and AERs remained elevated up to 20 years after the first melanoma. This study shows significantly increased long-term risks (both relative and absolute) of developing a second invasive melanoma after a first melanoma (invasive and in situ) which might serve as a basis for follow-up guidelines.

Geurts et al estimated, in a *commentary*, the expected impact of prolonged follow-up of patients with a history of invasive melanoma on health care services. They concluded that extension of follow-up period will result in overdiagnosis, overtreatment, anxiety in patients and a tripled workload for dermatologists. In our *rebuttal letter*, we agree that prolonged follow-up may have negative side effects and associated costs. In our opinion the duration and frequency of follow-up visits remain debatable and more research is needed to clarify the influence of follow-up visit schemes on melanoma survival and quality of life of melanoma survivors.

In **chapter 5** we describe the cumulative risk, Standardized Incidence Ratio and Absolute Excess Risk of subsequent different skin cancers in The Netherlands. A total of 50,510 melanoma patients and 64,054 patients with a squamous cell carcinoma of the skin were included (national data Netherlands Cancer Registry). The regional data of the Eindhoven Cancer Registry consisted of 5,776 melanoma patients, 5,749 SCC patients and 41,485 BCC patients. The 21-year cumulative risk of getting a subsequent melanoma after a first SCC or BCC was respectively 1.7% and 1.3% for males and 1.3% and 1.2% for females; SCC after melanoma or BCC was 4.6% and 9.3% (males) and 2.6% and 4.1%

(females); BCC after melanoma or SCC was respectively 13.2% and 27.8% (males) and 14.9% and 21.1% (females). SIRs and AERs remained elevated up to 21 years after the first melanoma, SCC or BCC. This study shows significantly increased long-term risks of developing a subsequent different skin cancer after a first melanoma, SCC or BCC. These estimates can serve as a base for follow-up guidelines and patient education.

In **chapter 6** we report a *commentary* on: Exclusive development of a single type of keratinocyte skin cancer: evidence from an Australian population-based cohort study (Keim et al). Major strengths of this study are 16 years of follow-up time, a clear case definition (i.e., histopathologically confirmed KC), the performed full-body skin examinations and detailed information on clinical features. The main limitations of this study were the small sample of patients with multiple cutaneous malignancies and the relatively young study population (the majority of the included people had not yet reached the age in which KC incidence is highest). Investing in large cohort studies and consortia might increase the validity of observational findings and should stimulate scientists to investigate the underlying mechanisms in detail.

In **chapter 7** we estimate trends in melanoma incidence by sex, Breslow thickness (thin melanomas subdivided into 4 subgroups: < 0.25 mm, 0.25-0.49 mm, 0.50-0.74 mm, and 0.75-1.0 mm), age and location, and compare these with trends in subgroups of thicker melanomas (source: Netherlands Cancer Registry). Between 1994-2010, 34,156 persons were diagnosed with an in situ or thin melanoma. The European standardized rate (ESR) of in situ melanomas doubled for males and females with a recent steeper rise in incidence (EAPC 12.1% and 12.5%, respectively). ESR for thin melanomas amongst males approximately doubled with a steep, but non-significant acceleration compared to other thickness categories since 2006 for <0.25 mm melanomas (EAPC 26.3%). For female patients with thin melanomas the ESRs increased almost two-fold, except for <0.25 mm melanomas. The incidence rates of in situ, thin and thick melanomas increased similarly between 1994 and 2010. Recently steep increases were found for in situ melanomas and thin melanomas in men. A combination of increased ultraviolet exposure and therefore a 'true' increase, increased awareness, early detection, diagnostic drift and 'overdiagnosis' are likely causes for these rises.

In **chapter 8** we investigate the prevalence of actinic keratosis (AK), its risk factors and association with skin cancer in an elderly population. Within the Rotterdam Study, a Dutch population-based cohort study, full body skin examinations were performed among 2,061 participants aged 45 years or older. Of these cohort members (mean age 72 years), 21% had 1 to 3, 9% 4 to 9 and 8% ten or more AK. Prevalence of AK in the Rotterdam Study was 49% (95% CI 46%–52%) for men and 28% (26%–31%) for women.

Extrapolation suggested that approximately 1.4 of the 16 million Dutch citizens are affected with AK. Male sex, older age, light pigmentation status, severe baldness, skin wrinkling and high tendency for sunburn were significantly associated with number of AKs and extensive actinic damage (≥10 AKs) in the multivariate analyses. Especially bald males were at an increased risk of severe actinic skin damage (adjusted OR= 7.0). The group with no AKs had a lower positive history for skin cancer (including melanoma, SCC or BCC) than the group with 10 or more AKs. The prevalence of AK is very high, especially among elderly bald males, and the presence of severe actinic damage significantly increases a history of skin cancer. The prevention and management of AK is a true challenge for patients, physicians, and health care policy makers.

In **chapter 9** we describe conditional survival of melanoma in The Netherlands (source: Netherlands Cancer Registry). Conditional survival analysis is performed on patients who survived the preceding year(s). To assess prognosis of melanoma survivors according to gender and Breslow thickness, conditional five-year relative survival was calculated for lymph node negative melanoma patients and conditional one-year relative survival was analysed for melanoma patients with and without nodal involvement. Between 1994 and 2008, 40,050 patients developed a melanoma (stage I-III, of whom 6% with nodal involvement). Six to eight years after diagnosis, survival of patients with a 1-2 mm (T2) thick melanoma equalized the general population. Conditional five-year relative survival for patients with >4mm thick (T4) melanomas increased from about 60% at diagnosis to 90% at 7 years after diagnosis. Largest improvements were found in patients with thick melanomas and female patients with nodal involvement. The prognosis for melanoma survivors improved with each additional year of survival after diagnosis, except for patients with a ≤1mm thick melanoma, who never had any excess mortality during follow-up. Conditional survival of melanoma was better among females, among those with lower Breslow thickness, and nodal stage. Quantitative insight into conditional survival is useful for dermatologists, surgeons and oncologists to help planning optimal cancer surveillance. It gives a more optimistic message of their future to melanoma survivors than the traditional survival rates and could reduce anxiety concerning their melanoma diagnosis in the past.

In **chapter 10** we compared the survival probabilities of patients with multiple melanomas with the survival of patients with only one melanoma. We included data from the Netherlands Cancer Registry (NCR) of all patients with a diagnosis of invasive cutaneous melanoma between 1994 and 2009; these were followed until 2011. Cox proportional Hazard models, with time-varying covariates for multiple melanomas were used to illustrate differences in survival of single melanoma and multiple melanoma patients. We showed that patients with multiple melanomas have a 50% worse survival, indicating

the importance of surveillance of melanoma patients in order to detect subsequent melanomas in early stages.

In **chapter 11** the main findings of the studies presented in this thesis are discussed and placed into perspective. In addition, study limitations are described and recommendations for future research are given. The increasing incidence of multiple cutaneous (pre)-malignancies in The Netherlands is and remains a large burden for the current health care system and will only increase in the future. This thesis contributes to the current knowledge on the occurrence of multiple cutaneous malignancies and associated mechanisms of field cancerization and overdiagnosis and could therefore be used as material for patient education and follow-up strategies. More research is needed in the field of treatment choices and all stages of prevention to manage skin cancer optimally. Mechanistic studies investigating aetiology and genetics are needed to further reduce the burden of multiple skin cancers. Cost-effectiveness studies are required to reduce the pressure of skin cancer on the Dutch health care system and I suggest further studies investigating the role of different health care providers in the first, second and tertiary line in terms of diagnosis, treatment and follow-up.

Samenvatting

Hoofdstuk 1 is een algemene inleiding voor dit proefschrift. Huidkanker, de meest voorkomende vorm van kanker onder de Kaukasische bevolking, omvat een groot aantal types maligniteiten en ontwikkelt zich uit diverse verschillende cellen. De drie meest voorkomende cutane maligniteiten ontwikkelen zich uit melanocyten en keratinocyten (geordend in afnemende agressiviteit): melanoom, plaveiselcelcarcinoom (PCC) en basaalcelcarcinoom (BCC). Dit proefschrift focust zich alleen op deze vormen van kanker en hun voorlopers. De incidentie van de drie meest voorkomende huidkankers zijn nog steeds stijgende en per land bestaan er grote verschillen. De meerderheid van huidkankerpatiënten kent een relatief goede prognose en dit heeft daarom implicaties voor de behandeling, follow-up strategieën en risico's op het ontwikkelen van multipele cutane (pre)-maligniteiten. Belangrijke onderwerpen zoals follow-up en vroegdetectie van huidkanker blijven een onderwerp van debat. In dit proefschrift beschrijf ik de impact van multipele cutane maligniteiten en de consequenties voor patiënten, artsen en het zorgstelsel.

In **hoofdstuk 2** beschrijven we een systematische review met meta-analyse waarin de risico's (proporties, gestandaardiseerde incidentie ratio's [SIR] en cumulatieve risico's) op het krijgen van een melanoom, basaalcelcarcinoom (BCC) of plaveiselcelcarcinoom (PCC) worden beschreven bij patiënten die eerder werden gediagnosticeerd met een melanoom. In totaal werden 50 van de 233 gelezen artikelen geïncludeerd. Voor melanoompatiënten was de 'gepoolde' proportie voor het krijgen van een nieuw melanoom, BCC of PCC, respectievelijk 3,8% (n=47); 2,8% (n=5) en 1,0% (n=6). De 'gepoolde' SIR voor het krijgen van een melanoom, BCC of PCC voor patiënten die eerder een melanoom hadden was achtereenvolgend 10,4 (n=12); 4,6 (n=2) en 2,8 (n=2). Bij melanoompatiënten was het gemiddelde 20-jaars cumulatieve risico op een nieuw melanoom, BCC of PCC respectievelijk 5,4% (n=3); 14,0% (n=1) en 4,0% (n=1). Subgroep analyses toonden substantiële verschillen in de risico's wanneer continenten en onderzoeksopzet werden vergeleken. Concluderend, een voorgeschiedenis met een melanoom geeft een hoog risico op het ontwikkelen van een opvolgend melanoom (ongeveer tienvoudig hoger risico), en in mindere mate op een opvolgend BCC of PCC. Secundaire preventie lijkt dus van groot belang te zijn bij deze patiëntengroep. Deze informatie kan gebruikt worden voor zorgstelsels.

In **hoofdstuk 3** beschrijven we een systematische review met meta-analyse waarin de risico's (proporties, gestandaardiseerde incidentie ratio's [SIR] en cumulatieve risico's) op het krijgen van een basaalcelcarcinoom (BCC), plaveiselcelcarcinoom (PCC) of me-

lanoom worden beschreven bij patiënten die eerder werden gediagnosticeerd met een keratinocyt carcinoom (KC, inclusief BCC en PCC). In totaal werden 45 artikelen geïncludeerd. Voor BCC patiënten was de 'gepoolde' proportie voor het krijgen van een nieuw BCC, PCC of melanoom, respectievelijk 29,2%; 4,3% en 0,5%. De 'gepoolde' proportie voor het krijgen van een PCC, BCC of melanoom bij patiënten met een PCC in de voorgeschiedenis was achtereenvolgend 13,3%; 15,9% en 0,5%. De 'gepoolde' SIR voor het krijgen van een BCC, PCC of melanoom was 17,4; 3,2 en 2,4 voor patiënten die eerder een BCC hadden en 4,2; 15,0 en 2,7 voor patiënten die eerder een PCC hadden. In de subgroep analyses werden de grootste verschillen gevonden tussen de verschillende continenten (risico's Australië> Noord-Amerika>Europa). Concluderend, een voorgeschiedenis met een BCC of PCC geeft een hoog risico op het ontwikkelen van een opvolgend BCC of PCC, en in mindere mate op melanoom. Secundaire preventie (vroegdetectie van opvolgende episodes van de ziekte) lijkt dus van groot belang te zijn bij deze patiëntengroep. Zij dienen goed geïnformeerd te worden over hun toekomstig risico op meerdere huidtumoren.

In **hoofdstuk 4** onderzoeken wij risico's (cumulatieve risico's, gestandaardiseerde incidentie ratio's [SIR] en absolute excess risico's [AER]) op het ontwikkelen van een tweede primaire in situ of invasief cutaan melanoom bij Nederlandse melanoompatiënten tussen 1989 en 2008. In totaal werden er 10.765 in situ and 46.700 invasieve melanoompatiënten geincludeerd (bron: Nederlandse Kanker Registratie). Bij patiënten met een in situ of invasief melanoom was het 20-jaars cumulatieve risico op een tweede invasief melanoom respectievelijk 6,2% en 5,0%. Het relatieve risico (SIR) van het ontwikkelen van een melanoom na een melanoom was 12 tot 26 keer verhoogd ten opzichte van de algehele bevolking. Tot 20 jaar na het eerste melanoom bleven de SIR's en AER's verhoogd. Deze studie laat langdurig verhoogde risico's zien op het ontwikkelen van een tweede melanoom na een eerste melanoom. Deze risico's kunnen gebruikt worden als informatie voor follow-up richtlijnen.

Geurts et al beschreven in een *commentaar* wat de te verwachten impact op het zorgstelsel zou zijn van langdurige follow-up van melanoompatiënten. Zij concludeerden dat verlenging van follow-up zal resulteren in overdiagnose, overbehandeling, angst bij patiënten en een verdrievoudigde werklast voor dermatologen. In onze *reactie* geven wij aan dat wij het eens zijn met eventuele negatieve uitwerkingen van verlengde follow-up en de geassocieerde kosten. Wij zijn van mening dat de duur en frequentie van follow-up bezoeken nog steeds betwistbaar is en dat er meer onderzoek nodig is om te verhelderen wat de invloed van verscheidene follow-up schema's is op de overleving van melanoompatiënten en de kwaliteit van leven van melanoompatiënten die nog in leven zijn.

In **hoofdstuk 5** onderzoeken wij risico's (cumulatieve risico's, gestandaardiseerde incidentie ratio's [SIR] en absolute excess risico's [AER]) op het ontwikkelen van een ander type huidkanker na een eerste huidkanker tussen 1989 en 2009. In totaal werden 50.510 melanoom patiënten en 64.054 patiënten met een plaveiselcelcarcinoom (PCC) geïncludeerd (landelijke data Nederlands Kanker Registratie). De regionale data van de Eindhoven Kanker Registratie bestond uit 5.776 melanoom patiënten, 5.749 PCC patiënten en 41.485 basaalcelcarcinoom (BCC) patiënten. Bij patiënten met een eerste PCC of BCC waren de 21-jaars cumulatieve risico's op een opvolgend invasief melanoom respectievelijk 1,7% en 1,3% voor mannen en 1,3% en 1,2% voor vrouwen; PCC na melanoom of BCC: 4,6% en 9,3% (mannen) en 2,6% en 4,1% (vrouwen); BCC na melanoom of PCC: respectievelijk 13,2% en 27,8% (mannen) en 14,9% en 21,1% (vrouwen). SIR's en AER's bleven verhoogd tot 21 jaar na het eerste melanoom, PCC of BCC. Deze studie toont langdurige significant verhoogde risico's op het ontwikkelen van een opvolgende ander type huidkanker na een eerste melanoom, PCC of BCC. Deze waarden kunnen gebruikt worden voor follow-up richtlijnen en patiënteneducatie.

In **hoofdstuk 6** rapporteren wij een commentaar op een artikel van Keim et al over het ontwikkelen van multipele huidkankers van een type. De kracht van deze studie is de 16 jaar aan follow-up tijd, een heldere definitie van de ziektegevallen (histopathologisch bevestigde keratinocyte carcinomen, de verrichte volledige huidinspecties en de gedetailleerde informatie over de klinische kenmerken van de patiënten. De belangrijkste beperkingen van de studie zijn de kleine aantallen patiënten met multipele cutane maligniteiten en de relatief jonge studie populatie (de meerderheid van de geïncludeerde patiënten had nog niet de leeftijd bereikt waarop de incidentie van keratinocyt carcinomen het hoogst is). Investeringen in grote cohort studies en consortia kan de validiteit van observationele bevindingen vergroten en zou wetenschappers moeten stimuleren om de onderliggende mechanismen in detail te onderzoeken.

In **hoofdstuk 7** onderzoeken wij incidentietrends van dunne melanomen in Nederland waarbij wij stratificeren voor geslacht, Breslow dikte (dunne melanomen onderverdeeld in 4 subgroepen: < 0,25 mm, 0,25-0,49 mm, 0,50-0,74 mm, and 0,75-1,0 mm), leeftijd en locatie en deze trends vergelijken met subgroepen van dikkere melanomen (bron: Nederlands Kanker Registratie). Tussen 1994 en 2010 werden er 34.156 mensen gediagnosticeerd met een in situ of dun melanoom. De naar de Europese standaardbevolking gestandaardiseerde incidentiecijfers (ESR) van in situ melanomen verdubbelden voor mannen en vrouwen met een recente steilere stijging in incidentie (de EAPC, de geschatte jaarlijkse procentuele verandering van het incidentiecijfer berekend op basis van jaarlijkse incidentiecijfers in de desbetreffende periode, was respectievelijk 12,1% en 12,5%). De ESR voor dunne melanomen bij mannen verdubbelde en toonde sinds

2006 een niet-significante (vergeleken met andere Breslow dikte categoriën) steile acceleratie voor melanomen dunner dan 0.25 mm (EAPC 26,3%). Voor vrouwen met dunne melanomen verdubbelden de ESR's bijna, behalve voor de melanomen dunner dan 0,25 mm. De incidenctiecijfers van in situ, dunne en dike melanomen stegen ongeveer gelijk tussen 1994 en 2010. Recent namen de incidentiecijfers van in situ melanomen en dunne melanomen bij mannen sterk toe. Een combinatie van verhoogde ultraviolet blootstelling (en dus een 'echte' stijging), een verhoogd bewustzijn, vroegdetectie, diagnostische drift en 'overdiagnose' zijn mogelijke oorzaken van deze stijgingen.

In **hoofdstuk 8** onderzoeken wij binnen een oudere populatie de prevalentie van actinische keratoses (AK's), de hiermee geassocieerde risicofactoren en de associatie met huidkanker. Bij 2061 deelnemers van 45 jaar en ouder (gemiddelde leeftijd 72 jaar) van de Rotterdam Study werd een volledig huidonderzoek uitgevoerd. Hiervan bleek 21% 1 tot en met 3 AK's te hebben, 9% 4 tot en met 9 en 8% 10 of meer. De AK prevalentie binnen de Rotterdam Study was 49% (95%BI 46%-52%) voor mannen en 28% (26%-31%) voor vrouwen. Extrapolatie van deze data toonde aan dat bijna 1.4 van de 16 miljoen Nederlanders AK heeft. Mannen, oudere leeftijd, lichte pigmentatie status, kaalheid, rimpels in het gezicht en gevoeligheid voor zonnebrand waren allen significant geassocieerd met ernstige actinische schade (≥10 AK's) in de multivariate analyses. Vooral kale mannen hadden een verhoogd risico op ernstige actinische schade (aangepaste odds ratio = 7,0 [3,8-13,1]). De groep deelnemers zonder AK's hadden minder vaak een voorgeschiedenis met een BCC, PCC of melanoom vergeleken met de groep deelnemers met tien of meer AK's. Concluderend kan er gezegd worden dat de prevalentie van AK's erg hoog is, vooral bij oudere kale mannen, en dat de aanwezigheid van ernstige actinische schade het risico op een huidkanker voorgeschiedenis verhoogd. De preventie en het management van AK's is en zal een uitdaging worden voor patiënten, artsen en gezondheidszorg medewerkers.

In **hoofdstuk 9** beschrijven wij de conditionele overleving van melanoom in Nederland (bron: Nederlandse Kanker Registratie). Conditionele overlevingsanalyse bepaalt de overleving van patiënten met een melanoom, naarmate zij langer leven na de diagnose. Alle patiënten die in de periode 1994-2008 de diagnose 'invasief melanoom' kregen, werden geïncludeerd. De prognose van melanoompatiënten werd berekend voor elk extra overleefd jaar na de diagnose, in de vorm van een conditionele relatieve 1- en 5-jaarsoverleving (de laatste alleen voor lymfekliernegatieve patiënten). Er werd uitgesplitst naar geslacht en Breslow-dikte. In de periode 1994-2008 werden 40.050 patiënten gediagnosticeerd met een melanoom (stadium I-III, 6% met lymfekliermetastasen). De overleving voor patiënten met een melanoom met een Breslow-dikte van ≤ 1,0 mm (T1) was op het moment van diagnose en gedurende de gehele follow-upperiode gelijk

aan die in de algehele bevolking. Zes tot acht jaar na diagnose werd de conditionele 5-jaarsoverleving van patiënten met een 1-2 mm dik melanoom (T2) ongeveer gelijk aan die van de algehele bevolking. Hoewel de conditionele relatieve 5-jaarsoverleving van patiënten met een melanoom > 4 mm dik (T4) steeg van ongeveer 60% bij diagnose naar 90% na 7 jaar, bleef een oversterfte van ongeveer 10% bestaan. Naarmate de patienten langer overleefden, werd de prognose van de Nederlandse melanoompatiënten beter, vooral bij lymfeklierpositieve vrouwen en patiënten met een dik melanoom. Bij patiënten met een T1-melanoom bleef de overleving vanaf diagnose gelijk aan die in de algehele bevolking. Deze cijfers geven een optimistischere en werkelijkheidsgetrouwere boodschap aan patiënten met een melanoom dan de traditionele relatieve overlevingscijfers, waardoor patiënten die overleven na de diagnose 'melanoom' misschien minder angst en praktische problemen ervaren.

In **hoofdstuk 10** onderzoeken we de overleving van patiënten met multipele melanomen in Nederland (bron: Nederlands Kanker Registratie). Wanneer er rekening wordt gehouden met de tijd tussen de melanomen in een Cox Proportional Hazards model in de vorm van een tijdsafhankelijke variabele dan wordt de hazard ratio van multipele versus een enkel melanoom 50% hoger. Deze studie toont de complexiciteit van overlevingsanalyses van multipele kankers en illustreert het belang van surveillance bij patiënten met een melanoom om nieuwe melanomen vroegtijdig te ontdekken.

In **hoofdstuk 11** worden de belangrijkste bevindingen van dit proefschrift besproken en in perspectief geplaatst. Daarnaast worden studie beperkingen beschreven en suggesties voor toekomstig onderzoek gegeven. De stijgende incidentie van multipele cutane (pre)-maligniteiten is en zal een uitdaging worden voor het huidige zorgstelsel. Dit proefschrift draagt bij aan de huidige kennis over het voorkomen van multipele cutane maligniteiten en de geassocieerde mechanismen van veld transformatie tot kanker en overdiagnose. Deze gegevens kunnen gebruikt worden voor patiënteneducatie en follow-up strategieën. Er is meer onderzoek nodig in het veld van behandelingskeuzes en alle stadia van preventie om het steeds omvangrijkere maatschappelijke gezondheidsprobleem huidkanker aan te kunnen. Bovendien zijn er mechanistische studies nodig die de etiologie en genetica onderzoeken om de impact van multipele huidkankers verder te verminderen. Kosteneffectiviteitsanalyses zijn nodig om de druk van huidkanker op het Nederlandse zorgstelsel te verminderen en toekomstige studies zouden de rol van verschillende zorgverleners in de eerste, tweede en derde lijn moeten onderzoeken op het vlak van diagnose, behandeling en follow-up.

Part V

Appendices

A. List of abbreviations
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C. List of Publications
D. Curriculum Vitae
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List of abbreviations

AER	absolute excess risk
AJCC	American Joint Committee on Cancer
AK	actinic keratosis
ALM	acrolentiginous melanoma
BCC	basal cell carcinoma
CI	confidence interval
CR	cumulative risk
CRS	conditional relative survival
EAPC	estimated annual percentage change
ECR	Eindhoven Cancer Registry
ERGO	Het Erasmus Rotterdam Gezondheid Onderzoek
ESR	European standardized rate
F	females
FBSE	full body skin examination
HR	hazard ratio
ICD-O	International Classification of Diseases for Oncology
IQR	interquartile range
KC	keratinocyte carcinoma
LM	lentigo maligna
M	males
Mel	melanoma
MMS	Mohs' micrographic surgery
N	number
N+	nodal involvement
N0	no nodal involvement
NA	not applicable
NCR	Netherlands Cancer Registry
NM	nodular melanoma
NMSC	non-melanoma skin cancer
NOS	Newcastle – Ottowa score
OR	odds ratio
Ref	reference group
RS	Rotterdam Study
SCC	squamous cell carcinoma
SD	standard deviation

SIR	standardised incidence ratio
SN	Sentinel Node
SSE	skin self-examination
SSM	superficial spreading melanoma
TNM	tumor lymph node metastasis
USA	United States of America
UV	ultraviolet
WSR	world standardized rate

List of co-authors

AFFILIATIONS AT THE TIME AT WHICH THE RESEARCH WAS CONDUCTED

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Institute of Psychology, Erasmus University Rotterdam, Rotterdam, the Netherlands

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Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands
National Cancer Institute, Directorate for Research, Prevention and Surveillance, Bogotá, Colombia

Judith Zoutendijk
Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

List of publications

PUBLICATIONS IN THIS THESIS

van der Leest, Liu, Coebergh, Neumann, Mooi, Nijsten, de Vries. Risk of second primary in situ and invasive melanoma in a Dutch population-based cohort: 1989-2008.
Br J Dermatol. 2012 Dec;167(6):1321-30

van der Leest, Nijsten, de Vries. Screening for second primary melanomas: is it efficient? Reply from authors.
Br J Dermatol. 2013 May;168(5):1135

Flohil, **van der Leest**, Arends, de Vries, Nijsten. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis.
Eur J Cancer. 2013 Jul;49(10):2365-75

Flohil, **van der Leest**, Dowlatshahi, Hofman, de Vries, Nijsten. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study.
J Invest Dermatol. 2013 Aug;133(8):1971-8

van der Leest, van Steenbergen, Hollestein, de Vries, Nijsten, van Akkooi, Janssen-Heijnen, Coebergh. Conditional survival of malignant melanoma in The Netherlands: 1994-2008.
Eur J Cancer. 2014 Feb;50(3):602-10

van der Leest, Flohil, Arends, de Vries, Nijsten. Risk of subsequent cutaneous malignancy in patients with prior melanoma: a systematic review and meta-analysis.
J Eur Acad Dermatol Venereol. 2014 Dec 10

Verkouteren, **van der Leest**, Nijsten. Cohort studies (and skin cancer) never come alone.
J Invest Dermatol. 2015 Mar;135(3):649-51

van der Leest, Hollestein, Liu, Nijsten, de Vries. Risks of different skin tumor combinations after a first melanoma, squamous cell carcinoma and basal cell carcinoma: Dutch population based cohort 1989 – 2009.
(submitted)

van der Leest, Zoutendijk, Nijsten, Mooi, van der Rhee, de Vries, Hollestein. Time trends of thin melanomas in The Netherlands, 1994 – 2010.
(submitted)

Pardo Cortes, **van der Leest**, Hollestein, Liu, Soerjomataram, de Vries, Nijsten. Survival of patients with single or multiple primary melanomas in the Netherlands: 1989 – 2009.
(in preparation)

OTHER PUBLICATIONS

Hajdarbegovic, **van der Leest**, Thio, Neumann. Dermatologische oncologie.
Analyse, Juni 2009

van der Leest, Koljenovic, Thio. E-learning cases vasculitis.
Website Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV); 2010

Hajdarbegovic, **van der Leest**, van der Snoek, Thio. Herpes simplex lymphangitis.
Nederlands Tijdschrift voor Dermatologie en Venereologie 2010 20:6(354-355)

van der Leest, de Vries, Bulliard, Paoli, Peris, Stratigos, Trakatelli, Maselis, Situm, Pallouras, Hercogova, Zafirovik, Reusch, Olah, Bylaite, Dittmar, Scerri, Correia, Medenica, Bartenjev, Guillen, Cozzio, Bogomolets, del Marmol. The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010.
J Eur Acad Dermatol Venereol. 2011 Dec;25(12):1455-65

Stratigos, Forsea, **van der Leest**, de Vries, Nagore, Bulliard, Trakatelli, Paoli, Peris, Hercogova, Bylaite, Maselis, Correia, del Marmol. Euromelanoma: a dermatology-led European campaign against nonmelanoma skin cancer and cutaneous melanoma. Past, present and future.
Br J Dermatol. 2012 Aug;167 Suppl 2:99-104

Liu, Soerjomataram, Nijsten, van der Aa, **van der Leest**, Coebergh, de Vries. Trends in the risks of melanoma as a second primary cancer among cancer patients in the Netherlands, 1989-2008.
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van der Leest, Hollestein, van Steenbergen, de Vries, Nijsten, van Akkooi, Coebergh en Janssen-Heijnen. Overleven met een melanoom: prognose op verschillende momenten na de diagnose.
Ned Tijdschr Geneeskd. 2014;158:A7592

Suppa, Altomare, Cannavò, Capizzi, Catricalà, Colombo, Fargnoli, Fossati, Frascione, Lisi, Santini, Scalvenzi, Peris; Italian investigators for the Euromelanoma prevention campaign Collaborators (23) Amerio, Antonini, Aste, Ayala, Bernengo, Bongiorno, Borroni, Bottoni, Calzavara-Pinton, Camplone, Chimenti, Crosti, Dattola, Delfino, Fabbri, Fanti, Filosa, Kostaki, Menni, Micali, Mozzillo, **van der Leest**, Vena. The Italian Euromelanoma Day: evaluation of results and implications for future prevention campaigns.
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Hajdarbegovic, Atiq, **van der Leest**, Thio, Nijsten. Atopic dermatitis is not a protective factor for melanoma but asthma may be.
Int J Clin Oncol. 2014 Aug;19(4):708-11

Sanders, **van der Leest**, Molhoek-de Rooij, Erceg. Blisters and post-inflammatory hyperpigmentation after cryolipolysis treatment in a darker-skinned female.
(submitted)

BOOK CHAPTERS

Hajdarbegovic, **van der Leest**, Munte, Thio, Neumann. Neoplasms of the facial skin.
Clin Plast Surg. 2009 Jul;36(3):319-34

Hajdarbegovic, **van der Leest**, den Hollander, Thio. Chapter 14 Cutaneous manifestations of Diabetes Mellitus.
Skin as a marker of underlying disease, Hall and Hall, 2010

van der Leest, Hajdarbegovic, Neumann. Chapter 7 Atopic Eczema in Ethnic Skin.
Textbook of Ethnic Dermatology (2012, Edited by Dr. Hamerlinck, Prof. Dr. J.R.M.G. Lambert, Prof. Dr. H.A.M. Neumann)

Curriculum Vitae

Robert (Robertus Josephus Theodorus) van der Leest is op 30 juni 1985 geboren te Oss. In 2003 behaalde hij zijn gymnasium diploma aan het Titus Brandsma Lyceum te Oss. Hetzelfde jaar werd hij door middel van decentrale selectie geplaatst voor de studie geneeskunde aan de Erasmus Universiteit Rotterdam en ging hij in Rotterdam wonen. Tijdens zijn studie was hij van 2004 tot 2007 werkzaam in het studententeam van de afdeling Longziekten en Dermatologie. Na zijn reguliere co-schappen begon hij in 2008 aan zijn afstudeeronderzoek onder leiding van Dr. H.B. Thio op de afdeling Dermatologie van het Erasmus Medisch Centrum te Rotterdam. In 2009 liep hij ook zijn oudste co-schap op deze afdeling. Op 11 september 2009 behaalde hij zijn arts-examen en van september 2009 tot juni 2011 was hij werkzaam als arts-onderzoeker op de afdeling Dermatologie van het Erasmus MC. Op 1 juli 2011 werd hij toegelaten tot de opleiding tot dermatoloog bij Professor Dr. H.A.M. Neumann in het Erasmus MC. Van 2010 tot en met 2015 werkte hij aan zijn proefschrift onder de begeleiding van Dr. E. de Vries, Dr. L.M. Hollestein en Professor Dr. T. Nijsten. In de periode 2010 tot heden hield hij zich bezig met klinische trials, Euromelanoma, het nieuwe blok Dermatologie in het Erasmus Rotterdam Gezondheid Onderzoek (ERGO), Dermato-Epidemiologie en verschillende klinische stages voor de opleiding tot Dermatoloog in het Erasmus MC te Rotterdam (opleiders Dr. H.B. Thio en Mr. Dr. E.R.M. de Haas) en het Amphia ziekenhuis te Breda (opleider Dr. A. Erceg).

Dankwoord

Dit proefschrift was nooit tot stand gekomen zonder de hulp, wijze raad en luisterende oren van een groot aantal mensen.

Allereerst wil ik mijn copromotor Dr. E. de Vries bedanken voor het opstarten van mijn promotietraject en de fantastische begeleiding de afgelopen jaren. Esther, jouw betrokkenheid bleef van begin tot eind, zowel professioneel als persoonlijk, ondanks de geografische afstand, even groot. Dankzij jouw enthousiasme, ideeën voor nieuwe projecten, altijd snelle nakijkwerk en antwoorden op mijn vragen heb ik mijn promotie naast de opleiding tot dermatoloog kunnen voltooien.

Mijn promotor Prof. Dr. T. Nijsten ben ik dankbaar voor de mogelijkheid om onderzoek te doen in het destijds recent gestarte dermatologie-ERGO-team. Tamar, het is een eer om in jouw dermatologie-epidemiologie groep te werken. Mijn promotie was een hobbelig traject, maar door jouw ingenieuze klinische blik op onderzoek hebben we uiteindelijk toch iets moois neergezet. Ik vind het inspirerend wat je in korte tijd hebt bereikt en wil je bedanken voor je wijze adviezen en begeleiding.

Dr. L.M. Hollestein, mijn tweede copromotor, was een fantastische hulp bij het voltooien van de tweede helft van mijn proefschrift. Loes, ook al waren de analyses soms om te huilen, door jouw enthousiasme en precisie was het toch leuk en werden de papers statistisch verantwoord. Ik vond het fijn om de laatste maanden op donderdag naast je te kunnen werken op jouw kamer, jouw drive en harde werken waren een grote stimulans.

Prof. Dr. H.A.M. Neumann, u gaf mij de mogelijkheid om in september 2009 te starten met onderzoek op de afdeling Dermatologie in het Erasmus MC. Ik kijk met mooie herinneringen terug naar alles wat u organiseerde voor zowel de arts-assistenten en onderzoekers en ik bewonder uw dermatologische kennis. Door uw mensenkennis en adviezen ben ik de afgelopen jaren ontzettend gegroeid, zowel op de werkvloer als persoonlijk. Hartelijk dank voor uw vertrouwen, steun en interesse.

Prof. Dr. H.A.M. Neumann, Prof. Dr. C. Verhoef en Prof. Dr. H.J. de Koning, dank voor uw bereidheid om plaats te nemen in de kleine commissie en voor het beoordelen van mijn proefschrift. Daarnaast wil ik de overige leden van de promotiecommissie Prof. Dr. V.E.P.P. Lemmens, Prof. Dr. W. Bergman, Prof. Dr. P.J.E. Bindels en Prof. Dr. V. del Marmol hartelijk danken voor de bereidheid om plaats te nemen in de grote commissie. Prof. Dr. W. Bergman, fijn dat u ondanks het nog steeds niet voltooide gezamenlijke project

toch opponent wilt zijn (hoofdstuk 5 is de boosdoener). Prof. Dr. V. del Marmol, thank you for being a member of the doctoral examination board and thanks for the great collaboration in 2010 and 2011, Euromelanoma was of major importance for the start of my scientific career.

Veel dank aan alle medewerkers van de Nederlandse Kanker Registratie en Eindhoven Kanker Registratie, Gitty Jaanen voor de precieze data-selectie, en Prof. Dr. J.W.W. Coebergh voor de leerzame en kritische commentaren. Medewerkers van het ERGO-centrum: ik vond het erg leuk om met jullie samen te werken.

Lifang Liu thanks for your help in the analyses and drafts, now I 'became' Dr. Bob. Alexander van Akkooi en Arjen Joosse, ik vond het leuk om jullie regelmatig te spreken op meetings en congressen. Cynthia Holterhues, wat was het leuk om samen onderzoek te doen.

Alle co-auteurs wil ik bedanken voor de goede samenwerking en al het statistische-, schrijf-, en correctiewerk (in het bijzonder: Prof. Dr. L.R. Arends, Dr. L.N. van Steenbergen, Prof. Dr. W.J. Mooi, Dr. L.M. Pardo Cortes en Judith Zoutendijk).

Sophie en Emmilia, jullie zijn geweldige paranimfen én collega's. De cirkel is rond, ik ben blij dat het uiteindelijk ook mij is gelukt. Sophie, jouw discipline, tempo en planning waren een inspiratie voor mij. Ook al werden we bijna niet goed van ons tweeluikje, we hebben veel lol gehad en gesmuld. Emmilia, bedankt voor de pep talks en gezelligheid. Het was altijd fijn om het met je over de moeilijkheden te hebben van het promoveren naast de opleiding (vanaf nu zullen we hopelijk nooit meer tot laat schrijven op de polikliniek en gaan we op tijd naar huis!). Jullie promotiewijsheden maakten het voor mij gemakkelijker om te weten wat ik wanneer moest plannen. Ik ben trots dat jullie tijdens de verdediging naast me staan en ben gelukkig met onze vriendschap. Enes, bij jou ben ik begonnen als afstudeeronderzoeker en kort daarna werden we collega's. We hebben zowel op als buiten de werkvloer een hoop geweldige dingen meegemaakt. Ook bij problemen sta je altijd voor me klaar. Ik hoop dat we nog veel humoristische momenten mogen meemaken.

Ik wil alle collega's van de polikliniek Dermatologie van het Erasmus MC en het Amphia ziekenhuis in Breda bedanken voor de prettige samenwerking. Lieve AIOS en onderzoekers (in het bijzonder: Leonie, Joris, Merel en Deepak), wat hebben we een leuk team. Ik ga nooit met tegenzin naar mijn werk en ik vind het fantastisch dat we regelmatig dingen doen na werktijd. Collega Dermatologen, bedankt voor jullie interesse en steun de afgelopen tijd. Barbera van Tienhoven, bedankt voor je hulp de afgelopen maanden.

Door de flexibiliteit van mijn opleiders Dr. H.B. Thio, Mr. Dr. E.R.M. de Haas en Dr. A. Erceg is het gelukt om te promoveren. Bing, ik wil jou ook bedanken voor je begeleiding tijdens de trials en de flexibiliteit om een andere weg in te slaan. Jouw feedback, kennis en humor zijn zeer waardevol voor mijn opleidingstijd. Mijn mentor, Dr. R.R. van den Bos, bedankt voor je adviezen en de fijne gesprekken.

Loes, Marloes en Duifje, ook al is het soms lastig om af te spreken door onze carrières, ik vind het altijd heerlijk om bij jullie te zijn. Hoe ouder we worden, hoe dieper onze vriendschap gaat. Ik ben super trots op jullie carrières, geniet van onze boerinnekeschat en hoop op nog veel mooie momenten samen.

Martijn, we zien elkaar niet vaak, maar als we elkaar zien is het goed. Bedankt voor je steun en interesse. Gerbrich, ik vind het nog steeds jammer dat ik je niet heb zien schitteren tijdens je verdediging. Hopelijk beleven we nog veel Roger-momenten samen.

Danielle, bedankt voor alle wijze adviezen, gezellige uitstapjes en het aanraden van de fantastische tekenaar van mijn kaft, Marcel Ruijters. Suzanne en Haidy, bedankt voor jullie interesse en de mooie momenten. Sjoerd, bedankt voor je hulp bij het maken van de letters voor de omslag.

Lieve schoonfamilie en aanhang, wat is het fijn om in jullie familie opgenomen te zijn. Dank voor alle begrip en steun. Lia, in deze hectische tijd hebben jouw lekkere maaltijden me op de been gehouden.

Lieve ouders, wat hebben jullie mij geweldig geholpen de afgelopen jaren. Jullie staan altijd voor me klaar met wijze raad en een luisterend oor. Het is een voorrecht om zo'n goede band met mijn ouders te hebben, wat was het fijn dat jullie mij af en toe in chaotische perioden als vanouds verzorgden (stiekem hoop ik dat sommige dingen nog lang door mogen gaan). Dit proefschrift draag ik dan ook op aan jullie. Edgar en Amanda, ik ben trots op jullie succesvolle carrières en wil jullie danken voor de waardevolle gedachtewisselingen. Edgar, hopelijk schrijven we in de toekomst samen een mooi Econometrisch-Medisch project.

There is only one … en daarom noem ik jou, lieve Alex, natuurlijk als laatste. We zijn nu al ruim 10 jaar samen en hebben samen veel meegemaakt. Ik ben super trots op de mooie zaak die je de afgelopen jaren hebt neergezet. Ik wil je bedanken voor je liefde, steun en het vertrouwen dat je me hebt gegeven tijdens mijn promotietraject. Vanaf nu zal ik geen werk meer meenemen op vakantie en verander ik van zuur in een zonnestraal (met mate uiteraard).

PhD Portfolio

Name PhD student:	Robert J.T. van der Leest
Department:	Erasmus MC University Medical Center, Department of Dermatology
PhD period:	2009-2015
Promotor:	Prof. Dr. T. Nijsten
Supervisors:	Dr. E. de Vries, Dr. L.M. Hollestein

	Year	Workload (Hours/ECTS)	Subtotal
1. PhD Training			
General academic skills			
- Academic writing and presentation skills (Proficiency level), Centre for British English, Rotterdam	2009	20 hours	
Research skills			
- DOO course communicatie	2012	8 hours	
- DOO course samenwerking	2011	8 hours	
- NIHES Erasmus Summer Programme 2011 ESP09 Regression Analysis	2011	1.9 ECTS	
- NIHES Erasmus Summer Programme 2011 ESP28 Survival Analysis	2011	1.9 ECTS	
- NIHES Erasmus Winter Programme 2010 EWP22 Biostatistics for Clinicians	2010	1.0 ECTS	
- NIHES Erasmus Winter Programme 2010 ESP01 Introduction to Clinical Research	2010	0.9 ECTS	
- Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK)	2010	22 hours	8 ECTS
Presentations – Oral			
- Risk of subsequent cutaneous malignancy in patients with prior melanoma: A systematic review and meta-analysis; 23rd EADV Congress Amsterdam, The Netherlands	2014	1 ECTS	
- The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010; Skintermezzo, Gerlos, Oostenrijk	2012	1 ECTS	
- Risk of second primary in situ and invasive melanomas in a population-based cohort; EADV congress, Lisbon, Portugal	2011	1 ECTS	
- The central database of Euromelanoma: Past, present and future 'Euromelanoma: First results Euromelanoma 2011'; EADV congress, Lisbon, Portugal	2011	1 ECTS	
- The Euromelanoma skin cancer prevention campaign in Europe: characteristics and results of 2009 and 2010; EORTC melanoma group meeting, Barcelona, Spain	2011	1 ECTS	

-	Risk of second melanomas in population-based cohort; EORTC melanoma group meeting, Brussels, Belgium	2011	1 ECTS	
-	Risico op tweede primair melanoom in Nederland; 12e wetenschappelijke jaarvergadering van de NVED, Lunteren	2011	1 ECTS	
-	Euromelanoma Europe 2009 & 2010, Results, analysis and discussion, EADV Göteborg, Sweden, Euromelanoma session	2010	1 ECTS	
-	Skintermezzo Klinische trials en promotieonderzoek, psoriasis trials, Rotterdam	2010	1 ECTS	9 ECTS
Presentations – Poster				
-	Time trends of thin melanomas in The Netherlands, 1994 – 2010: A systematic review and meta-analysis; 23rd EADV Congress Amsterdam, The Netherlands	2014	1 ECTS	
-	Time trends of thin melanomas in The Netherlands, 1994 – 2010; 8th World Congress of Melanoma (9th Congress of the EADO), Hamburg, Germany	2013	1 ECTS	
-	Risk of subsequent cutaneous malignancy in patients with prior melanoma and keratinocyte carcinoma: A systematic review and meta-analysis; 8th World Congress of Melanoma (9th Congress of the EADO), Hamburg, Germany	2013	1 ECTS	
-	Poster award for best poster presentation at the 6th International Congress on Dermato-Epidemiology (IDEA), Malmö, Sweden	2012	1 ECTS	4 ECTS
International conferences				
-	EADV Congress Amsterdam, The Netherlands	2014	1 ECTS	
-	SPA III: Oncologie in de parel van de Ardennen, Spa, Belgium	2014	1 ECTS	
-	8th World Congress of Melanoma (9th Congress of the EADO), Hamburg, Germany	2013	1 ECTS	
-	SPA II: Oncologie in de parel van de Ardennen, Spa, Belgium	2012	1 ECTS	
-	6th International Congress on Dermato-Epidemiology (IDEA), Malmö, Sweden	2012	1 ECTS	
-	20th Congress of the European Academy of Dermatology and Venereology (EADV), Lisbon, Portugal	2011	1 ECTS	
-	EORTC melanoma group meeting, Barcelona, Spain	2011	1 ECTS	
-	EORTC melanoma group meeting, Brussels, Belgium	2011	1 ECTS	
-	6th EADO (European Association of Dermatologic Oncology) congress, Greece, Athens	2010	1 ECTS	
-	SPA I: Oncologie in de parel van de Ardennen, Spa, Belgium	2010	1 ECTS	
-	19th Congress of the European Academy of Dermatology and Venereology (EADV), Gothenburg, Sweden	2010	1 ECTS	11 ECTS
National conferences				
-	PhD Weekend Dermatology Erasmus MC 2012, Schey, Zuid-Limburg	2012	16 hours	
-	DIO dagen, Abbott, Zeist	2012	16 hours	
-	30 Jaar Pigmented Lesion Clinic LUMC, Leiden	2012	6 hours	
-	12e Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2011	1 ECTS	
-	Comorbiditeit, een probleem bij psoriasis? Erasmus MC, Afdeling Dermatologie; Rotterdam, Nederland	2010	3 hours	

-	11e Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2010	1 ECTS	
-	10e Wetenschappelijke vergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, Lunteren, Nederland	2009	1 ECTS	
-	Autumn symposium 2009 Consultation center for Patient Oriented Research Cost-Effective Interventions in Health Care: From Evaluation to Application, Rotterdam	2009	3 hours	
-	Symposium Patients, People and Populations 40 years of Epidemiology at Erasmus, Rotterdam	2009	6 hours	
-	FEDERA Federatie van Medisch Wetenschappelijke Verenigingen (FMWV) Medisch Wetenschappelijke Dag – Veroudering en ouderdomskwalen – Scientific Program – Aging and the infirmities of old age: new insights and challenges! Leiden, Nederland	2009	8 hours	5 ECTS

Other

-	KWF meeting verstandig zonnen, Amsterdam	2015	3 hours	
-	Training Time-management, Utrecht	2013	1 ECTS	
-	DOO course ziekenhuismanagement	2013	16 hours	
-	Dermatoscopie cursus, Rotterdam, Nederland	2012	4 hours	
-	Dermatoscopie specialistische basis-cursus met e-learning, Leiden, Nederland	2011	8 hours	
-	Thema-avond IKNL 'Nieuwe ontwikkelingen binnen de diagnostiek en behandeling van het maligne melanoom'	2011	2 hours	
-	Thema-avond IKNL 'Alle risicofactoren voor huidkanker nogeens op een rij'	2011	2 hours	
-	Consultatiecentrum Patiëntgebonden Onderzoek (CPO) minicursus, Nederlands Architectuurinstituut, Rotterdam	2010	4 hours	
-	Dermatoscopie Boerhaave cursus, Leiden, Nederland	2010	8 hours	
-	The CADMUS Study, European Investigators meeting, Paris, France	2010	8 hours	
-	Phase Forward, InForm 4.5 PI Data Entry – Modules, Online learning Method	2010	2 hours	
-	Serious Adverse Event training, T. de Belder, Janssen-Cilag International NV	2010	4 hours	
-	Erasmus Medisch Centrum, Rotterdam: Autumn Symposium 2009, Cost-Effective Interventions in Health Care: From Evaluation to Application, Rotterdam	2009	4 hours	3 ECTS

Occasional reviewer for the following journals:

- British Journal of Dermatology
- European Journal of Cancer
- Journal of the European Academy of Dermatology and Venereology
- Nederlands Tijdschrift voor Geneeskunde

2. Teaching activities

Supervision of master's thesis:

-	Judith Zoutendijk	2013	1 ECTS	

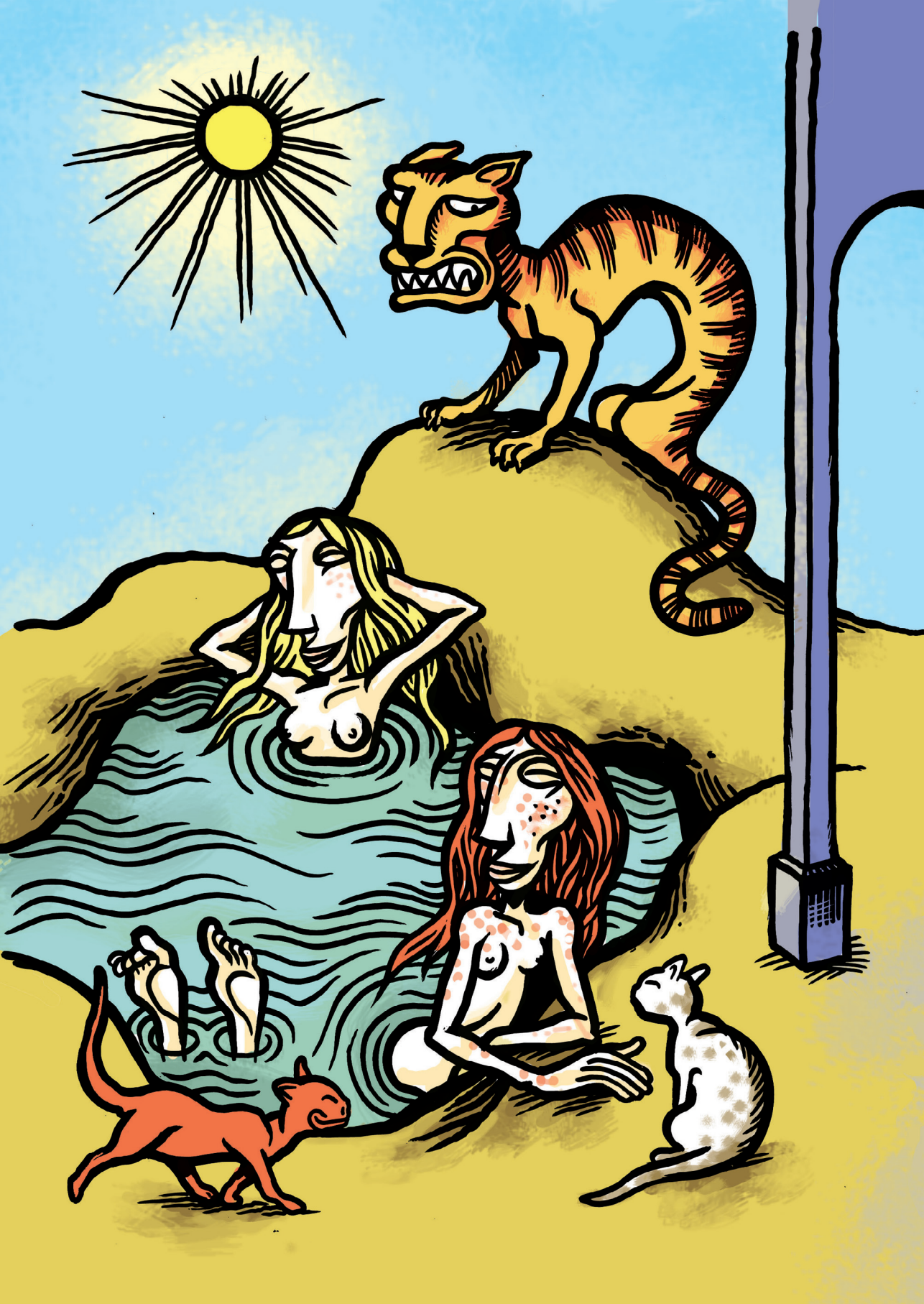
Other:

-	DOO course Teach the Teacher	2015	16 hours	
-	Teaching Assistant EADV fostering course 'Clinical Research and Epidemiology' - Practical data-analyis III	2014	6 hours	
-	Oral presentation methods hour: Meta-analysi(bia)s	2012	8 hours	
-	Teaching Assistant Summer Course for Dermatologists EADV / ESDR / EDEN Practical data-analysis (standardization, survival analysis).	2012	6 hours	

Organizational committee member of:

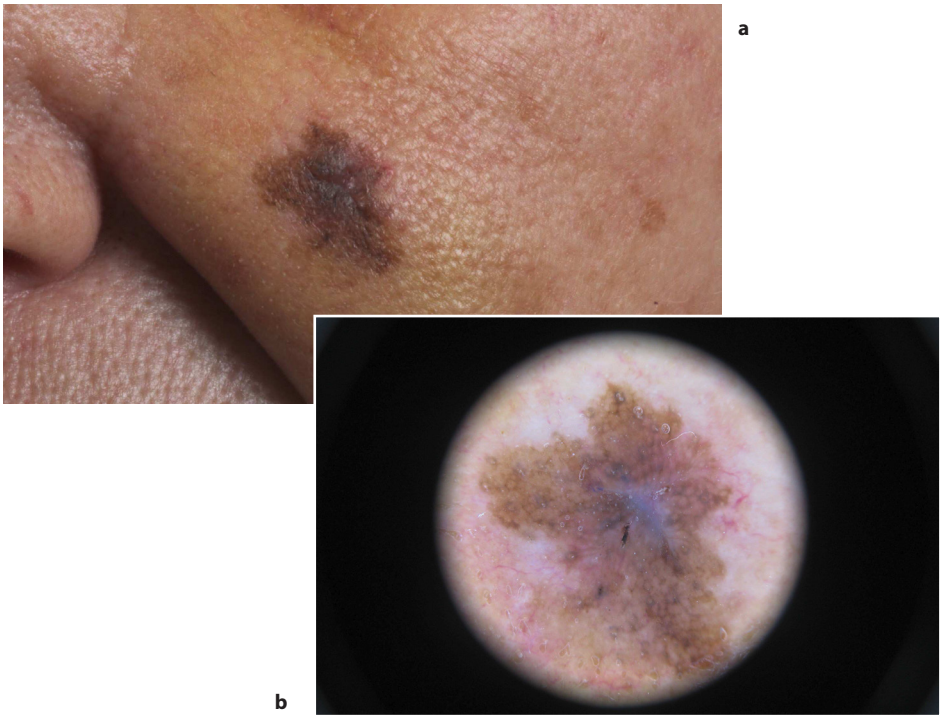
-	SPA II: Oncologie in de parel van de Ardennen, Spa, Belgium	2012	1 ECTS	
-	PhD Weekend Dermatology Erasmus MC 2012, Schey, Zuid-Limburg	2012	1 ECTS	
-	Cursus Dermoscopie Prof. L. Brochez en Dr. K. Vossaert	2012	8 hours	4 ECTS

Total: 44 ECTS

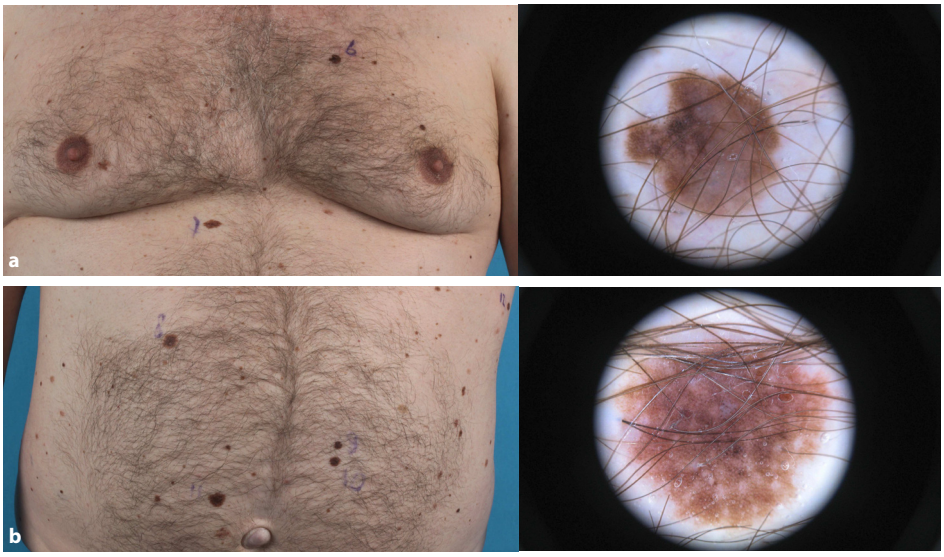



Multiple Cutaneous (pre)-Malignancies
Robert van der Leest

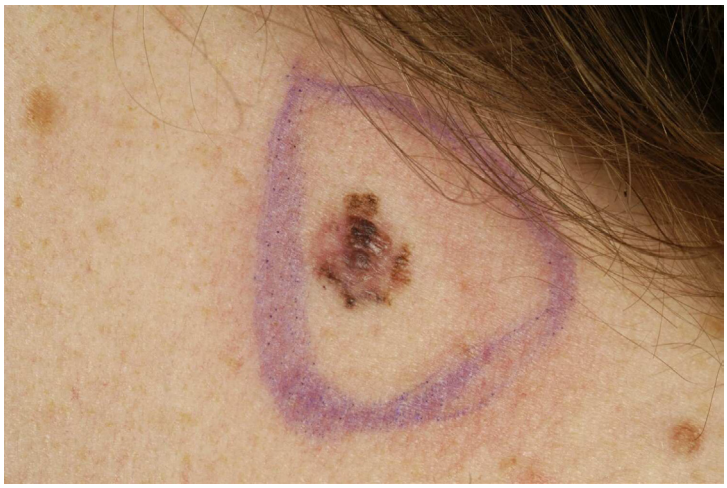
Color section



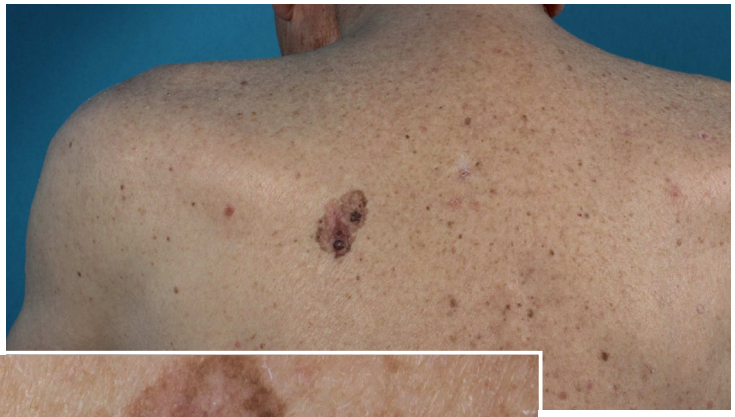
1ab Lentigo maligna / Melanoma in situ

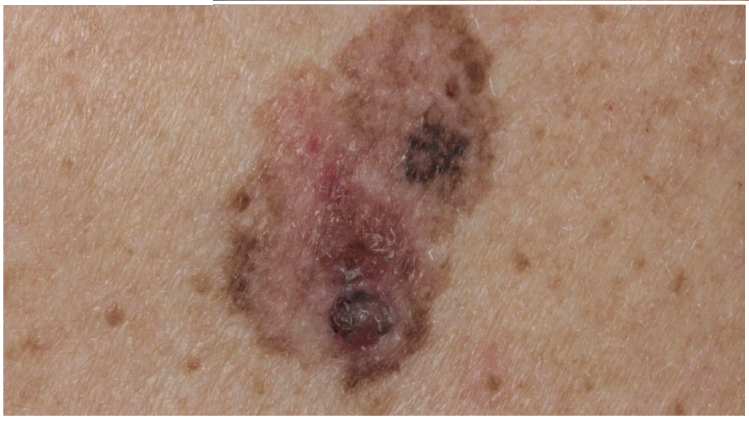


2a Melanoma in situ (6) **2b** Dysplastic nevi (8, 9, 10 and 11)

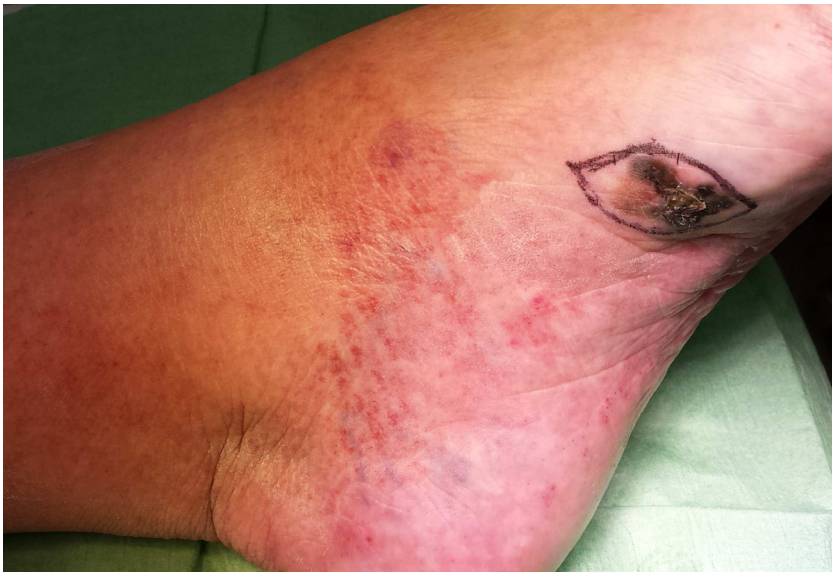


3 Superficial spreading melanoma (T1)

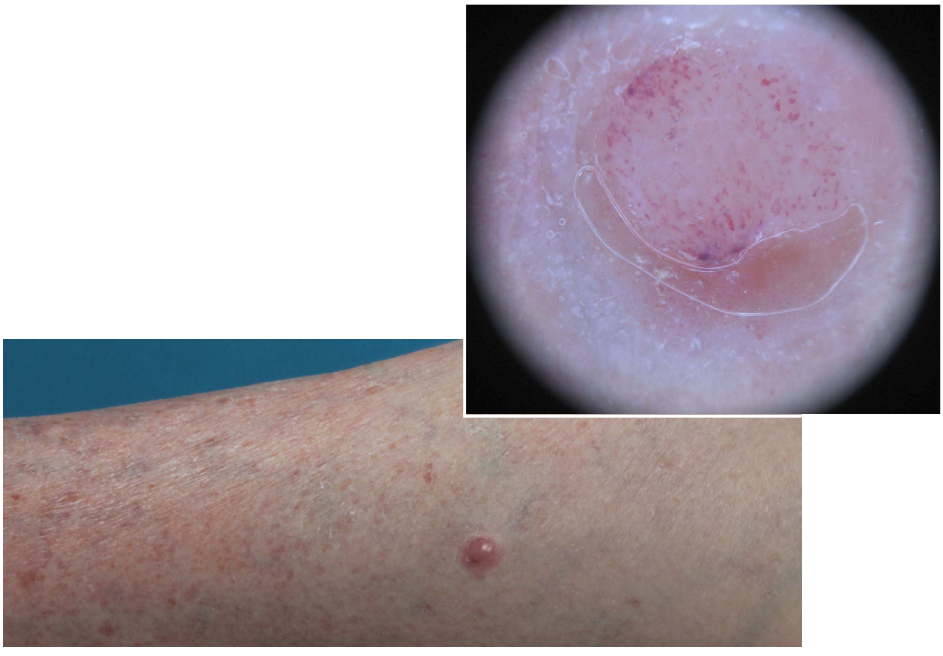




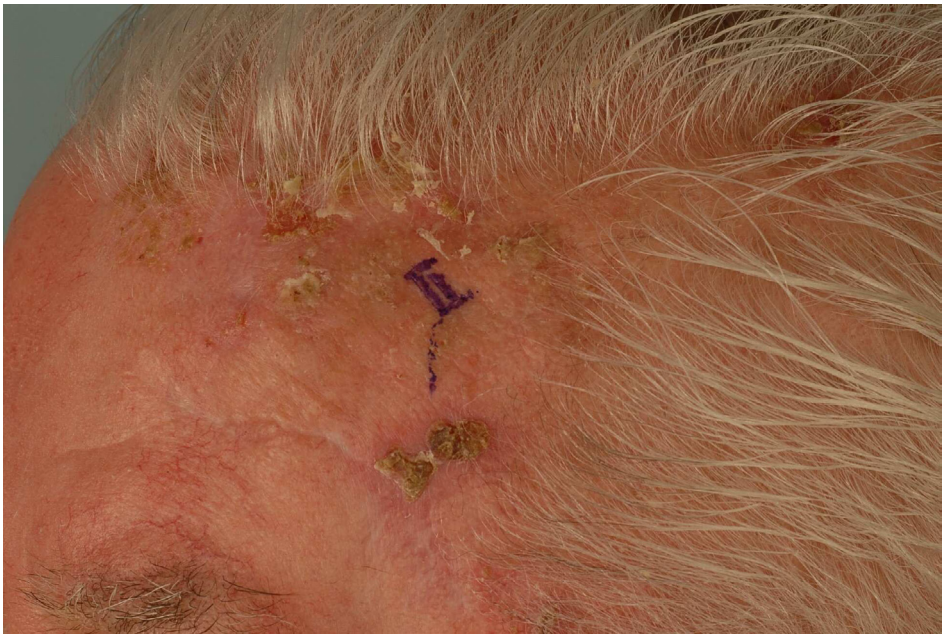
4 Nodular melanoma (T3)



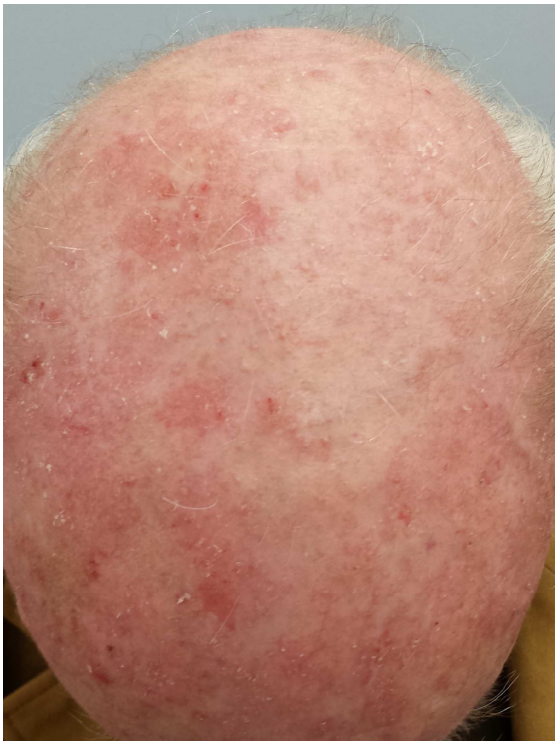
5 Acral melanoma (T3)



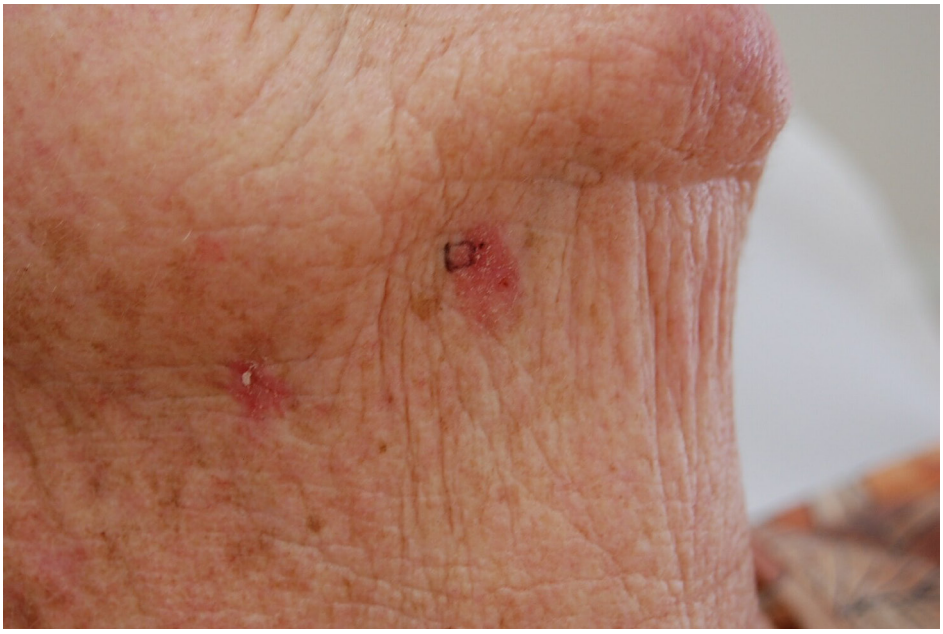
6ab Amelanotic nodular melanoma (T3)



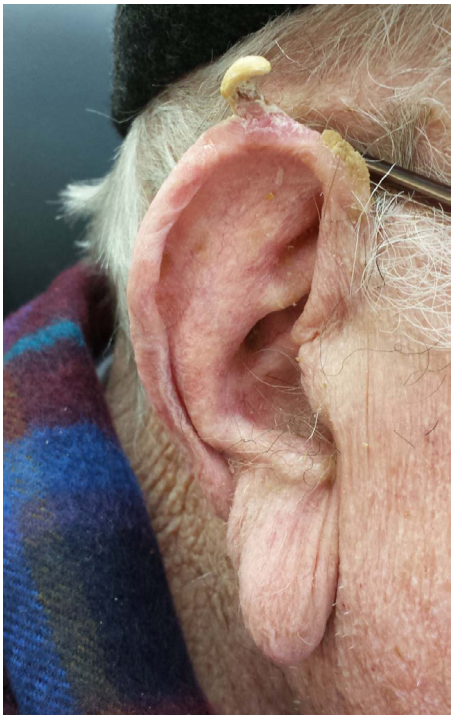
7 Actinic Keratosis



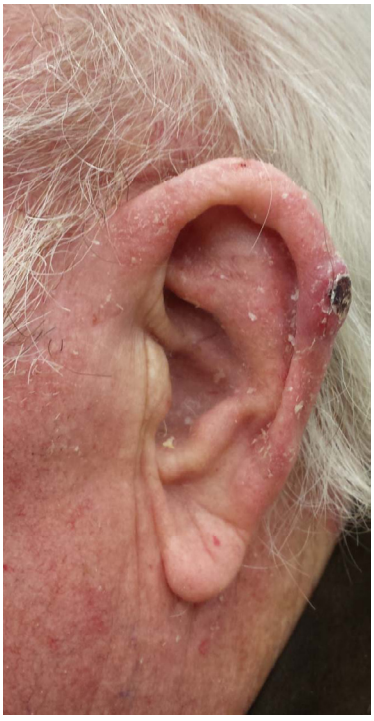
8 Multiple Actinic Keratoses, 'Field cancerization'



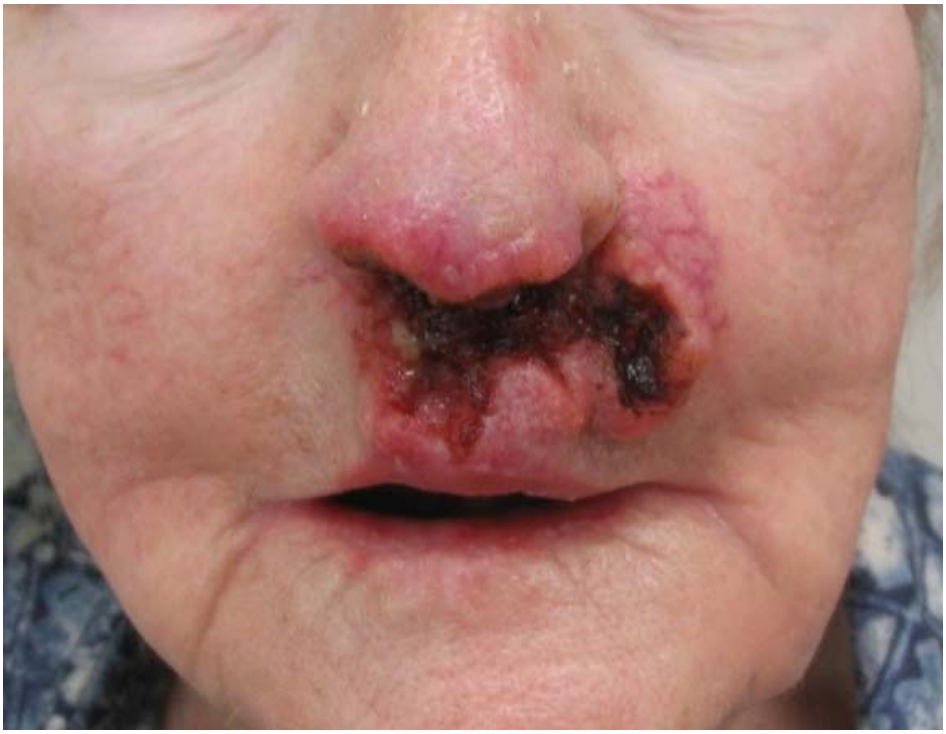
9 Morbus Bowen, Squamous Cell Carcinoma in situ



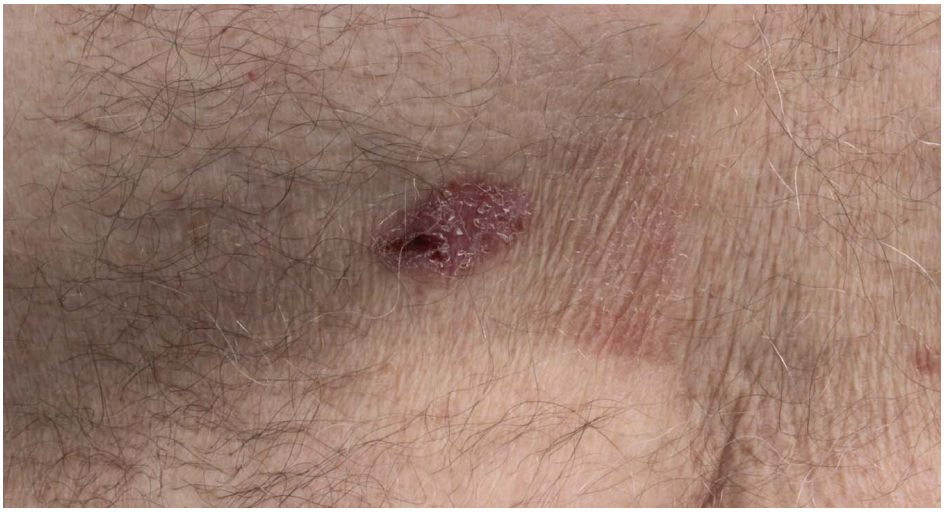
10 'Cornu cutaneum': Squamous Cell Carcinoma, well differentiated



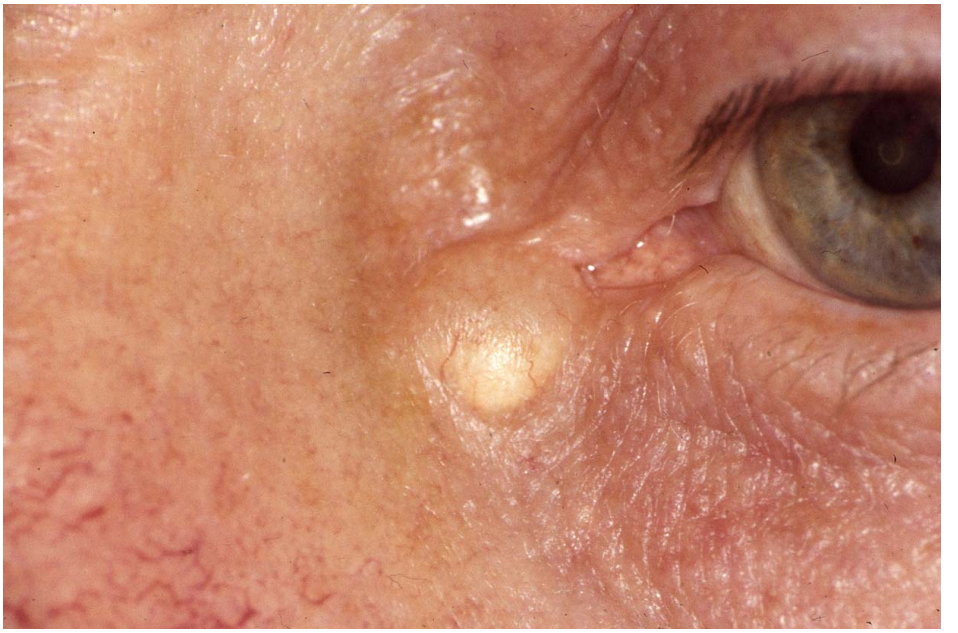
11 Squamous Cell Carcinoma, moderately differentiated



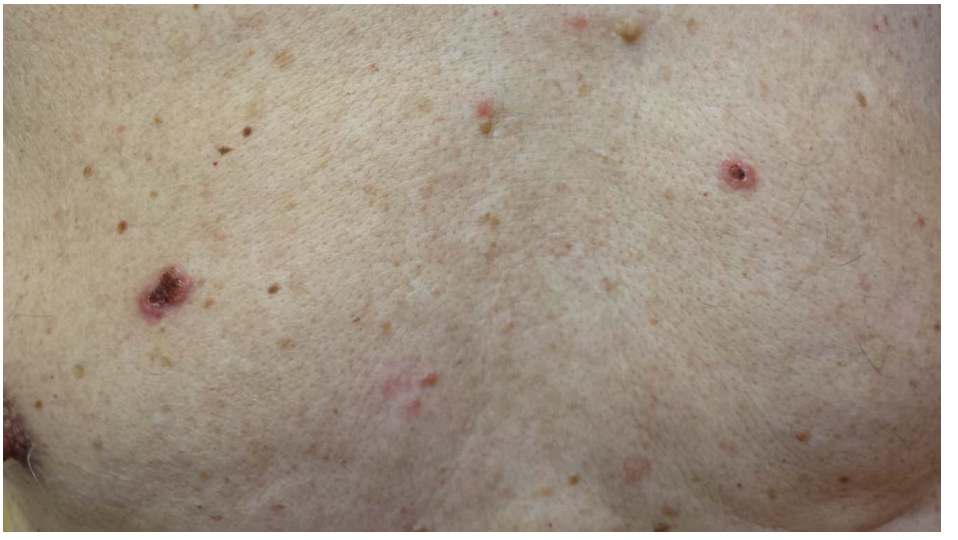
12 Squamous Cell Carcinoma, poorly differentiated



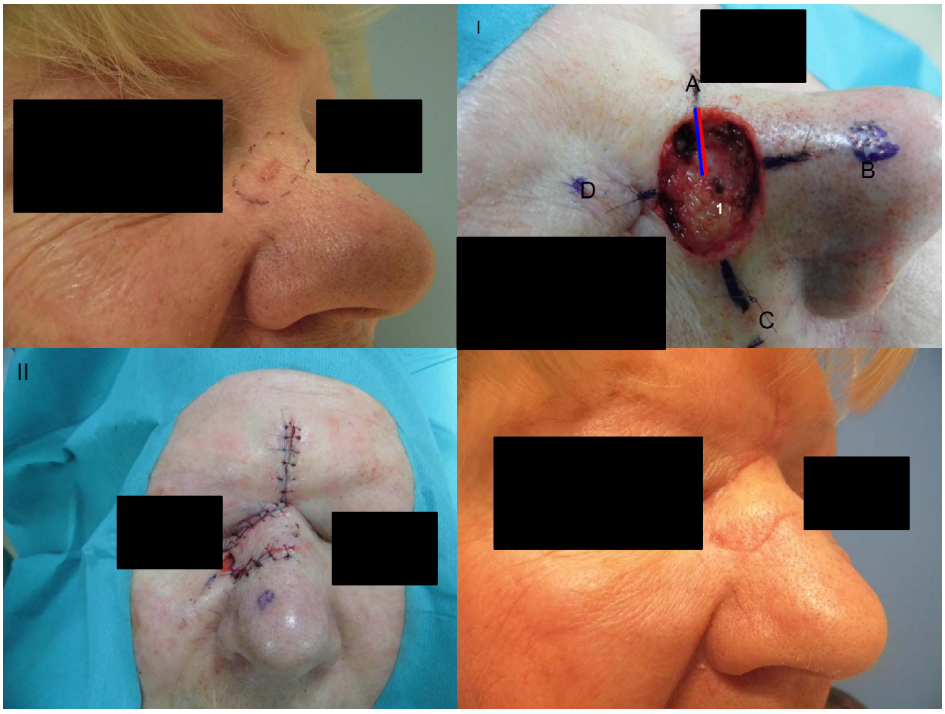
13 Superficial Basal Cell Carcinoma



14 Nodular Basal Cell Carcinoma



15 Two synchronous Nodular Basal Cell Carcinoma



16 Infiltrative Basal Cell Carcinoma treated with Mohs' Micrographic Surgery and a glabellar flap.

Financial support for this thesis was generously provided by:

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